

## **NOTE TO INSTRUCTORS**

Contact your Elsevier Sales Representative for teaching resources—including image banks—for this title, or request these supporting materials at <http://evolve.elsevier.com>



# NETTER'S ATLAS OF NEUROSCIENCE

3rd Edition

**David L. Felten, MD, PhD**

Chairman  
Clerisy Corporation  
Pittsford, New York

**M. Kerry O'Banion, MD, PhD**

Professor and Interim Chair  
Department of Neurobiology and Anatomy  
Director of the Medical Scientist Training Program  
University of Rochester School of Medicine  
Rochester, New York

**Mary Summo Maida, PhD**

Adjunct Professor of Neurobiology and Anatomy  
University of Rochester School of Medicine  
Rochester, New York

*Illustrations by*

**Frank H. Netter, MD**

*Contributing Illustrators*

**James A. Perkins, MFA, CMI, FAMI**

**Carlos A. G. Machado, MD**

**John A. Craig, MD**

ELSEVIER

# ELSEVIER

1600 John F. Kennedy Blvd.  
Ste. 1800  
Philadelphia, PA 19103-2899

NETTER'S ATLAS OF NEUROSCIENCE, THIRD EDITION

ISBN: 978-0-323-26511-9

Copyright © 2016, 2010, 2003 by Elsevier, Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: [www.elsevier.com/permissions](http://www.elsevier.com/permissions). This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Permission for Netter Art figures may be sought directly from Elsevier's Health Science Licensing Department in Philadelphia, PA: phone 1-800-523-1649, ext. 3276, or (215) 239-3276; or email [H.Licensing@elsevier.com](mailto:H.Licensing@elsevier.com).

## Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

International Standard Book Number: 978-0-323-26511-9

Senior Content Strategist: Elyse O'Grady  
Senior Content Development Specialist: Marybeth Thiel  
Publishing Services Manager: Patricia Tannian  
Senior Project Manager: John Casey  
Designer: Amy Buxton

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1



Working together  
to grow libraries in  
developing countries

[www.elsevier.com](http://www.elsevier.com) • [www.bookaid.org](http://www.bookaid.org)

# ABOUT THE AUTHORS

**DAVID L. FELTEN, MD, PhD**, is currently Chairman of the Board and Chairman of the Scientific and Medical Advisory Board for Clerisy Corporation, a biotech firm located in Pittsford, New York. He was formerly Vice President for Research and Medical Director of the Research Institute at William Beaumont Health System in Royal Oak, Michigan and the Founding Associate Dean for Research at Oakland University William Beaumont School of Medicine. He previously served as Dean of the School of Graduate Medical Education at Seton Hall University in South Orange, New Jersey; the Founding Executive Director of the Susan Samueli Center for Integrative Medicine and Professor of Anatomy and Neurobiology at the UC Irvine School of Medicine; the Founding Director of the Center for Neuroimmunology at Loma Linda School of Medicine; and the Kilian J. and Caroline F. Schmitt Professor and Chair of the Department of Neurobiology, and Director of the Markey Charitable Trust Institute for Neurobiology and Neurodegenerative Diseases and Aging at the University of Rochester School of Medicine in Rochester, New York. He received a bachelor of science degree from Massachusetts Institute of Technology and medical and doctoral degrees from the University of Pennsylvania School of Medicine. Dr. Felten carried out pioneering studies of autonomic innervation of lymphoid organs and neural-immune signaling that underlie the mechanistic foundations for psychoneuroimmunology and many aspects of integrative medicine.

Dr. Felten is the recipient of numerous honors and awards, including the prestigious John D. and Catherine T. MacArthur Foundation Prize Fellowship, two simultaneous NIH MERIT awards from the National Institutes of Mental Health and the National Institute on Aging, an Alfred P. Sloan Foundation Fellowship, an Andrew W. Mellon Foundation Fellowship, a Robert Wood Johnson Dean's Senior Teaching School Award, the Norman Cousins Award in Mind-Body Medicine, the Building Bridges of Integration Award from the Traditional Chinese Medicine World Foundation, and numerous teaching awards.

Dr. Felten co-authored the definitive scholarly text in the field of neural-immune interactions, *Psychoneuroimmunology* (Academic Press, 3rd edition, 2001) and was a founding co-editor of the major journal in the field, *Brain, Behavior and Immunity*, with Drs. Robert Ader and Nicholas Cohen of the University of Rochester School of Medicine. Dr. Felten is the author of more than 210 peer-reviewed journal articles and reviews, many on links between the nervous system and immune system. His work has been featured on Bill Moyer's PBS series and book, "Healing and the Mind," "20/20," and many other media venues. He served for over a decade on the National Board of Medical Examiners, including Chair of the Neurosciences Committee for the US Medical Licensure Examination.

**M. KERRY O'BANION, MD, PhD**, is Professor and Interim Chair of the Department of Neurobiology and Anatomy and Director of the Medical Scientist Training Program at the University of Rochester School of Medicine in Rochester, New York. He received a bachelor of science degree and medical and doctoral degrees from the University of Illinois at Champaign-Urbana. As a postdoctoral fellow at the University of Rochester, Dr. O'Banion cloned cyclooxygenase-2 and discovered its critical role in mediating inflammation.

Dr. O'Banion has worked for more than 20 years in the field of neuroinflammation, with particular interests in how cytokines mediate disease pathology. His current work, funded by NIH and NASA, focuses on possible beneficial effects of modulating inflammation in Alzheimer disease, the persistent effects elicited by brain irradiation, and the potential risk of neurodegenerative disease in individuals exposed to cosmic radiation.

Dr. O'Banion has authored nearly 120 peer-reviewed journal articles and reviews on these and other topics.

Since 1997, Dr. O'Banion has co-directed the Medical Neural Science course (now called Mind, Brain, and Behavior I) at the University of Rochester School of Medicine, a role he assumed from Dr. Felten. Dr. O'Banion also helped design and direct Mind, Brain, and Behavior II, a basic science course that accompanies medical clerkships in neurology and psychiatry for third-year medical students. He has been program director of the University of Rochester MSTP since 2000 and has served on multiple national committees related to medical and doctoral training.

**MARY E. MAIDA, PhD**, divides her time among research, teaching, mentoring future medical scientists, mentoring future entrepreneurs, and leading two companies focused on translational research. She is an adjunct faculty member of the Department of Neurobiology and Anatomy at the University of Rochester School of Medicine, as well as an annually invited Mentor for Entrepreneurship at the University of Rochester Simon School of Business. During her academic training she received bachelor of science degrees in microbiology/immunology and finance and operations management. She returned to academic medicine as a nontraditional student after having raised her children, commencing at the University of Miami School of Medicine and subsequently at the University of Rochester School of Medicine, where she completed a master of science degree in neurobiology and anatomy, and a doctoral degree in molecular neuroscience under the mentorship of Drs. M. Kerry O'Banion, John Olschowka, Richard Phipps, and Denise Figlewicz.

Because her return to medical and basic sciences training resumed after she raised her children, her interest turned from microbiology/immunology to the broader field of neuroimmunology, which seeks to pinpoint how the CNS and immune systems are intricately involved in a delicate and elaborate dance of connectivity, everyday cross-talk, more elaborate communication when pathogens or damage is involved, give-and-take vs. give-and-go between the two systems (and among other systems), and many more descriptions than words can adequately capture.

Dr. Maida has received several honors and awards across many disciplines, including Outstanding Alumni of Distinction Award from Excelsior College, New York State Hall of Distinction Award, Partners in Lifelong Learning Award, Greater Rochester Excellence in Achievement Technology Award, Winning Mentor for Mark Ain Business Competition, 43North Semifinalist distinction, and winning finalist in several open invitation awards.

A firm proponent of fostering and living the spirit-mind-body relationship that clearly underlies optimal neural-immune health, Dr. Maida is devoted to her family, her Catholic faith, and the privilege of being a Eucharistic Minister. She is honored to be a community volunteer and board member for agencies that support US military veterans and their families. She is a community volunteer and board of trustees member of agencies that care for medically fragile children and their families and has founded a scholarship fund at Excelsior College, named in honor of her parents. Dr. Maida is a fun-loving and enthusiastic competitor in tennis, running, golf, cross-fitness training, and equestrianism and a lover of the arts as a patron, musician, and active performer.

# DEDICATION

*In memory of Walle J.H. Nauta, MD, PhD, Institute Professor  
of Neuroscience at the Massachusetts Institute of Technology*

*A distinguished, brilliant, and pioneering neuroscientist  
An outstanding and inspirational teacher  
A kind, supportive, insightful, and gracious mentor  
An incredible role model and human being*

*and*

*To my wife, Mary E. Maida, PhD*

*A wonderful wife, partner, and friend  
My inspiration and motivation  
A superb researcher, teacher, scientific innovator, and CEO  
A woman who has it all—brains, beauty, kindness, and  
accomplishment*

**David L. Felten**

*In memory of Teresa Bellofatto, Nicholas Summo, and Robert  
Summo*

*Beloved family and friends who faced overwhelming health  
challenges with determination and a remarkably positive  
attitude.  
They showed the strength of the human spirit and the joy  
of human kindness in the face of daunting physiological  
odds.  
They taught us that it is possible to be healed in the absence  
of a cure.  
May their memory inspire us to continue to strive for a better  
understanding of the molecular, physiological, and sys-  
temic mechanisms that underlie health and disease.*

**David L. Felten  
Mary E. Maida**

*In memory of Fred Coyner and Nellie Rogers, sweet souls changed in old age, who turned my attention to brain dysfunction and neuroscience research*

*and*

*To my parents, Terry O'Banion and Mary Rogers, who both served as educators, teaching me the values of service in the name of learning and inspiring me to pursue my love of nature despite the piles of fossils, the stench of chemistry experiments, and some small fires they may still not know about.*

*and*

*To my spouse, Dorothy Petrie, also an educator, for her love, her unconditional support through late nights and weekends of writing and looming deadlines, and her consistent reminder that the opportunity to do science is a gift to be shared with all*

**M. Kerry O'Banion**

*In honor of my mother, Mary D. Summo, MS, who endlessly gave her love, time, talent, intellect, and wise advice to the 6 of us, her children, and her 10 grandchildren, and still does. Thank you, Mom.*

*and*

*In memory of my father, Dr. Anthony J. Summo, a true Renaissance man who embraced and promoted the reality of psychobiology, biopsychology, and PTSD well before they became accepted into mainstream medicine. And whose Ciba-Geigy Netter "green books" with the flip-over acetate pages sitting on our living room coffee table fascinated me and formed the basis of my love for science and medicine*

*and*

*To my husband, David L. Felten, MD, PhD, and my sons Michael and Matthew Maida, without whose love, encouragement, and support I would never be the woman I am today. In the spirit and words of our ancestors' family motto: Avanti! Sempre Avanti!*

**Mary E. Maida**

# ACKNOWLEDGMENTS

For decades, Dr. Frank Netter's beautiful and informative artwork has provided the visual basis for understanding anatomy, physiology, and relationships of great importance in medicine. Generations of physicians and healthcare professionals have "learned from the master" and have carried Dr. Netter's legacy forward through their own knowledge and contributions to patient care. There is no way to compare Dr. Netter's artwork to anything else because it stands in a class of its own. For many decades, the *Netter Collection* volume on the nervous system has been a flagship for the medical profession and for students of neuroscience. It was a great honor to provide the framework, organization, and new information for the updated first and second editions, and now the third edition, of *Netter's Atlas of Neuroscience*. The opportunity to make a lasting contribution to the next generation of physicians and healthcare professionals is perhaps the greatest honor anyone could receive.

I also gratefully acknowledge Walle J.H. Nauta, MD, PhD, whose inspirational teaching of the nervous system at MIT contributed to the organizational framework for this atlas. Professor Nauta always emphasized the value of an overview; the plates in the beginning of Section II, Regional Neurosciences, on the conceptual organization of sensory, motor, and autonomic systems, especially reflect his approach. I am particularly honored to contribute to these updated editions of *Netter's Atlas of Neuroscience* because I first learned neurosciences as an undergraduate in Professor Nauta's laboratory at MIT through his personal mentorship, masterful insights, and explanations—using the first *Nervous System* "green book" volume by Dr. Frank Netter. It is my hope that continuing generations of students can benefit from the legacy of this wonderful teacher and great scientist.

I thank our outstanding artist and medical illustrator, James Perkins, MS, MFA, for his clear, creative, and beautiful contributions to this revised atlas. Jim is an excellent anatomist, with great insights for bringing otherwise complex systems and mechanisms into understandable illustrations.

We thank Gabrielle A. Yeane, MD, Assistant Professor of Pathology, Division of Neuropathology, Department of Pathology, University of Rochester School of Medicine, for her preparation of brain stem cross sections from neuropathological specimens. These sections allow us to directly compare the previous illustrations with actual cross-sectional preparations used in neuropathology evaluations.

I thank Sasha Kurumety, now a student at Northwestern University, for her evaluation and summary of axonal transport, contributing to the new figure in Chapter 1.

Special thanks go to the outstanding editors at Elsevier Clinical Solutions: Marybeth Thiel, Senior Content Development Specialist, Elyse O'Grady, Senior Content Strategist, and John Casey, Senior Project Manager. They helped guide the process of the third edition and gave us the latitude to introduce new components, such as the many new molecular plates (especially in Chapter 1), photomicrographs, spinal cord and brain stem histological cross sections, and new clinical correlations.

I also would like to acknowledge my friend, colleague, and co-author of this atlas, Kerry O'Banion. His insights, spanning from the molecular details to the systemic interactions of neural systems, are amazing. For close to 30 years we have had the privilege of working together, both in teaching and research arenas. As one of the premier experts on brain inflammation and a highly knowledgeable molecular biologist, his expertise in this third edition has been invaluable.

Continuing thanks also go to Ralph Jozefowicz, MD, the consummate neurology educator. It was a delight to work with him in the University of Rochester medical neurosciences course and to learn from him through his amazing insights into clinical

neurology, and his ability to make those insights come alive for the benefits of both his students and colleagues.

And finally, to my wife Mary (Mary E. Maida), I again thank you for your unwavering love and your support and encouragement to continue this challenging project, and for your patience with the long hours and seemingly endless clutter of papers and folders you tolerated along the way. I particularly appreciate your willingness to personally join this effort as a co-author of the third edition. Your expertise as a molecular neuroscientist and your outstanding ability to take complex plates and explanations and help to clarify and re-express them in understandable terms for the readers has been a valuable addition.

**David L. Felten**

First, I thank David Felten not only for the opportunity to contribute to this third edition but also for his long-standing support, encouragement, and friendship. Second, I thank Ralph Jozefowicz, MD, Professor of Neurology at the University of Rochester, who together with David Felten served as outstanding mentors for how to teach neuroscience. Finally, I am indebted to my professional colleagues and students, past and current, for the opportunity to learn new things as we pursue science together.

**M. Kerry O'Banion**

To this very day, I remember my fascination with the original Netter “green books” that sat prominently displayed on the coffee table in the living room of my childhood home. I would sit for hours turning each page, which added another colorful layer to the beauty and intricacy of the human body’s anatomy and physiology—and day after day trying to recall what I saw, let alone make sense of it all. These original tomes that contained the original illustrations of Dr. Frank Netter in part formed the basis of my interest in, and pursuit of, science and medicine. It is an honor to be invited to participate, five decades later, as a contributor to the third edition of *Netter’s Atlas of Neuroscience*.

I thank my parents, Dr. Anthony J. and Mary D. Summo, for having provided us with such an enriched environment at home and for encouraging and allowing us to pursue our dreams.

I thank the University of Rochester School of Medicine and Dentistry Graduate Program in Neuroscience for providing me the opportunity to pursue my dreams as a nontraditional student. I also extend my deepest gratitude to my mentors M. Kerry O'Banion, MD, PhD, John Olschowka, PhD, Richard Phipps, PhD, and Denise Figlewicz, PhD, whom I have the privilege to know as friends as well as research colleagues.

Finally, I express my deepest gratitude to my husband, David Felten, and to my sons Michael and Matthew Maida—my biggest cheerleaders in life—who help me achieve far more than I believe I am capable of achieving and who adeptly help to keep my immune system healthy with the daily dose of humor and laughter we share.

**Mary E. Maida**



# PREFACE

As in the first and second editions, *Netter's Atlas of Neuroscience*, 3rd edition, combines the richness and beauty of Dr. Frank Netter's illustrations with key information about the many regions and systems of the brain, spinal cord, and periphery. Jim Perkins and John Craig have contributed additional outstanding illustrations to complement the original Netter illustrations.

The first edition included cross-sectional illustrations through the spinal cord and brain stem, as well as coronal and axial (horizontal) sections. The second edition built on the first edition with several additional illustrations and extensive new imaging using computed tomography (CT), magnetic resonance imaging (MRI), both T1- and T2-weighted, positron emission tomography (PET) scanning, functional MRI (fMRI), and diffusion tensor imaging (DTI), which provides pseudocolor images of central axonal commissural, association, and projection pathways. Full-plate MRIs were included for direct side-by-side comparisons with Dr. John Craig's illustrations of the brain stem cross sections and axial and coronal sections. More than 200 "clinical boxes" were added to offer succinct clinical discussions of the functional importance of key topics. These clinical discussions were intended to assist the reader in bridging the anatomy and physiology depicted in each relevant plate to important related clinical issues.

This third edition has many new components. Chapter 1, in the Overview section, "Neurons and Their Properties," has been extensively revised and reorganized. Approximately 15 new plates on molecular and cellular topics such as astrocytes, microglia, oligodendrocytes, axonal transport, growth and trophic factors, nuclear transcription factors, neuronal stem cell biology, and others have been added. Almost 50 new plates have been added throughout the atlas. Many of these plates reflect Jim Perkins' outstanding ability to represent molecular and cellular concepts in lucid and beautiful form. We have added histological cross sections of the spinal cord and brain stem to match the previous illustrations. We also added brain stem sections illustrating the major vascular syndromes of the medulla, pons, and midbrain. Many new photomicrographs have been introduced to plates throughout the atlas to add clarity to the illustrations.

The third edition retains the organization of the first and second editions: (I) Overview, (II) Regional Neurosciences, and (III) Systemic Neurosciences. Further breaks in these sections into component chapters aid in ease of use. We have provided succinct figure legends to point out some of the major functional aspects of each illustration, particularly as they relate to problems that a clinician may encounter in the assessment of a patient with neurological symptoms. We believe that it is important for an atlas of the depth and clarity of *Netter's Atlas of Neuroscience* to let the illustrations provide the focal point for learning, not long and detailed written explanations that constitute a full textbook in itself. However, the figure legends, combined with the excellent illustrations and the clinical discussions, provide content for a thorough understanding of the basic components, organization, and functional aspects of the region or system under consideration.

*Netter's Atlas of Neuroscience* provides a comprehensive view of the entire nervous system, including the peripheral nerves and their target tissues, central nervous system, ventricular system, meninges, cerebral vascular system, developmental neuroscience, and neuroendocrine regulation. We have provided substantial but not exhaustive details and labels so that the reader can understand the basics of human neuroscience, including the nervous system information usually presented in medical neurosciences courses, the nervous system components of anatomy courses, and neural components of physiology courses in medical school.

We are confronted with an era of rapid changes in health-care and exploding knowledge in all fields of medicine, particularly with the continuing revolution in molecular biology. Medical school curricula are under enormous pressure to add more and more non-basic sciences components. It has become dangerously tempting to emphasize high-technology tests, readouts, and imaging as a substitute for the real foundations of medical practice—the history and the physical examination. Many medical schools strive to “decompress” the intensity of teaching and to incorporate more problem-based and small group teaching exercises (which we applaud), with a goal of hastening students into clinical experiences.

In the long run, much of the additional information crammed into the medical curriculum has come at the expense of the basic sciences, particularly anatomy, physiology, histology, and embryology. We believe that there is a fundamental core of knowledge that every physician must know. It is not sufficient for a medical student to learn only 3 of the 12 cranial nerves, their functional importance, and their clinical applications, as “representative examples,” in order to further reduce the length of basic sciences courses. Although medical students are always anxious to get into the clinics and see patients, they need a substantial fund of knowledge to be even marginally competent, particularly if they strive to apply evidence-based practice, instead of rote memory, to patient care.

## ORGANIZATION OF NETTER'S ATLAS OF NEUROSCIENCE

The Overview section of the atlas is a presentation of the basic components and organization of the nervous system, a “view from 30,000 feet”; this view is an essential foundation for understanding the details of regional and systemic neurosciences. The Overview includes chapters on neurons and their properties, an introduction to the forebrain, brain stem and cerebellum, spinal cord, meninges, ventricular system, cerebral vasculature, and developmental neuroscience.

The Regional Neurosciences section provides the structural components of the peripheral nervous system, the spinal cord, the brain stem and cerebellum, and the forebrain (diencephalon and telencephalon). We begin in the periphery and move from caudal to rostral. The peripheral nervous system section includes details about the somatic and autonomic innervation of peripheral nerves; we do not leave the learner at the boundary of CNS and PNS, and hope that they can find out about peripheral and autonomic nerves from a gross anatomy course. This detailed regional understanding

is necessary to diagnose and understand the consequences of a host of lesions whose localization depends on regional knowledge—this includes strokes, local effects of tumors, injuries, specific demyelinating lesions, inflammatory reactions, and many other localized problems. In this section many of the clinical correlations assist the reader in integrating a knowledge of the vascular supply with the consequences of infarcts (e.g., brain stem syndromes), which requires a detailed understanding of brain stem anatomy and relationships.

The Systemic Neurosciences section evaluates the sensory systems, motor systems (including cerebellum and basal ganglia, acknowledging that they also are involved in many other spheres of activity besides motor), autonomic-hypothalamic-limbic systems (including neuroendocrine), and higher cortical functions. We have organized each sensory system, when appropriate, with a sequential presentation of reflex channels, cerebellar channels, and lemniscal channels, reflecting Professor Nauta's conceptual organization of sensory systems. For the motor systems, we begin with lower motor neurons and then show the various systems of upper motor neurons followed by cerebellum and basal ganglia, whose major motor influences are ultimately exerted through regulation of upper motor neuronal systems. For the autonomic-hypothalamic-limbic system, we begin with the autonomic preganglionic and postganglionic organization and then show brain stem and hypothalamic regulation of autonomic outflow, and finally limbic and cortical regulation of the hypothalamus and autonomic outflow. The systemic neurosciences constitute the basis for carrying out and interpreting the neurological examination. We believe that it is necessary for a student of neuroscience to understand both regional organization and systemic organization. Without this dual understanding, clinical evaluation of a patient with a neurological problem would be incomplete.

In a discipline as complex as the neurosciences, the acquisition of a solid organization and understanding of the major regions and hierarchies of the nervous system is not just a “nice idea” or a luxury—it is essential. The fact that this approach has been stunningly successful for our students in a course organized and taught for 15 years by both authors of the first edition (David L. Felten, MD, PhD and Ralph F. Jozefowicz, MD), and by M. Kerry O'Banion, MD, PhD and Ralph F. Jozefowicz, MD, for more than 15 years is an added benefit but is not why we organized this *Atlas* as we have. A working competence for students in basic and clinical neuroscience, and its value for delivering outstanding patient care, are always the main focus of our efforts. We truly value success in this arena. Knowledgeable and highly competent students are the finest outcome of our teaching that we could ever achieve. We hope that our students will come to appreciate both the beauty and the complexity of the nervous system and be inspired to contribute to the knowledge and functional application to patients of this greatest biological and medical frontier, which constitutes the substrate for human behavior and our loftiest human aspirations and endeavors.

David L. Felten

# ABOUT THE ARTISTS

**FRANK H. NETTER, MD** was born in 1906 in New York City. He studied art at the Art Students League and the National Academy of Design before entering medical school at New York University, where he received his medical degree in 1931. During his student years, Dr. Netter's notebook sketches attracted the attention of the medical faculty and other physicians, allowing him to augment his income by illustrating articles and textbooks. He continued illustrating as a sideline after establishing a surgical practice in 1933, but he ultimately opted to give up his practice in favor of a full-time commitment to art. After service in the United States Army during World War II, Dr. Netter began his long collaboration with the CIBA Pharmaceutical Company (now Novartis Pharmaceuticals). This 45-year partnership resulted in the production of the extraordinary collection of medical art so familiar to physicians and other medical professionals worldwide.

In 2005, Elsevier, Inc. purchased the Netter Collection and all publications from Icon Learning Systems. There are now more than 50 publications featuring the art of Dr. Netter available through Elsevier, Inc. (in the US: [www.us.elsevierhealth.com/Netter](http://www.us.elsevierhealth.com/Netter); outside the US: [www.elsevierhealth.com](http://www.elsevierhealth.com)).

Dr. Netter's works are among the finest examples of the use of illustration in the teaching of medical concepts. The 13-book *Netter Collection of Medical Illustrations*, which includes the greater part of the more than 20,000 paintings created by Dr. Netter, became and remain one of the most famous medical works ever published. Dr. Netter's *Atlas of Human Anatomy*, first published in 1989, presents the anatomical paintings from the *Netter Collection*. Now translated into 16 languages, it is the anatomy atlas of choice among medical and health professions students the world over.

The Netter illustrations are appreciated not only for their aesthetic qualities, but, more important, for their intellectual content. As Dr. Netter wrote in 1949, "... clarification of a subject is the aim and goal of illustration. No matter how beautifully painted, how delicately and subtly rendered a subject may be, it is of little value as a medical illustration if it does not serve to make clear some medical point." Dr. Netter's planning, conception, point of view, and approach are what inform his paintings and what makes them so intellectually valuable.

Frank H. Netter, MD, physician and artist, died in 1991.

Learn more about the physician-artist whose work has inspired the Netter Reference collection: <http://www.netterimages.com/artist/netter.htm>.

**CARLOS MACHADO, MD** was chosen by Novartis to be Dr. Netter's successor. He continues to be the main artist who contributes to the Netter Collection of medical illustrations.

Self-taught in medical illustration, cardiologist Carlos Machado has contributed meticulous updates to some of Dr. Netter's original plates and has created many paintings of his own in the style of Netter as an extension of the Netter collection. Dr. Machado's photorealistic expertise and his keen insight into the physician/patient relationship inform his vivid and unforgettable visual style. His dedication to researching each topic and subject he paints places him among the premier medical illustrators at work today.

Learn more about his background and see more of his art at: <http://www.netterimages.com/artist/machado.htm>.

**JAMES A. PERKINS, CMI, FAMI** is Professor of Medical Illustration at Rochester Institute of Technology (RIT) where he teaches courses in anatomy, digital illustration, and scientific visualization. He is a Board Certified Medical Illustrator and Fellow of the Association of Medical Illustrators.

An expert in visualizing biological processes, Professor Perkins has illustrated more than 40 medical textbooks, particularly in the areas of pathology, physiology, and molecular biology. For more than 20 years, he has been the sole illustrator of the “Robbins” series of pathology texts published by Elsevier, including the flagship of the series, *Robbins and Cotran Pathologic Basis of Disease*. He has been a contributor to the Netter Collection since 2001, creating most of the new art for *Netter’s Atlas of Human Physiology*, *Netter’s Illustrated Pharmacology*, and *Netter’s Atlas of Neuroscience* and contributing to many other titles.

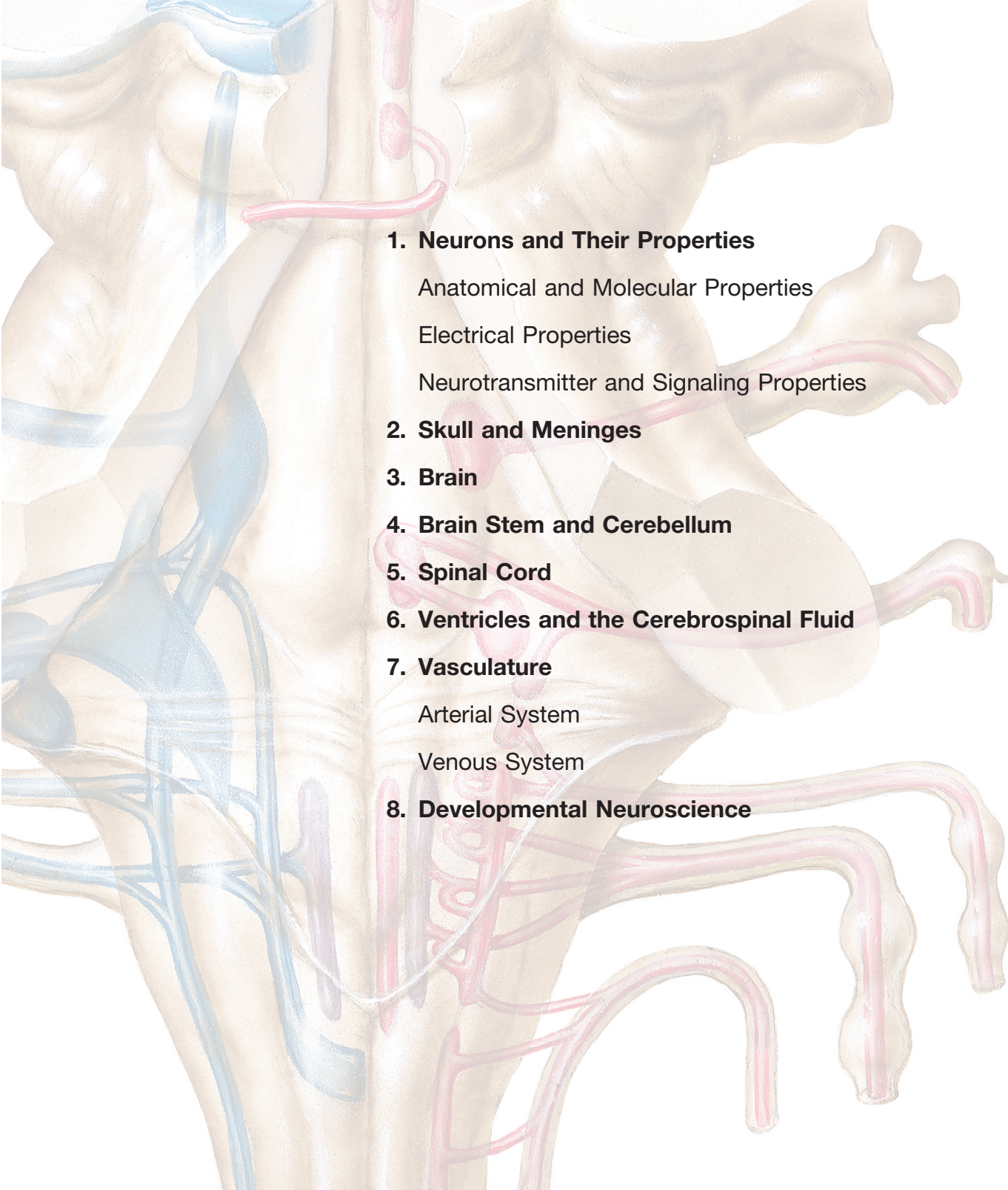
Professor Perkins received a bachelor degree in biology and geology from Cornell University and studied vertebrate paleontology and anatomy at the University of Texas and University of Rochester. He received a Master of Fine Arts degree in medical illustration from RIT and spent several years working in medical publishing and the medical legal exhibit field before returning to RIT to join the faculty. Learn more about his background and see more of his art at: <http://www.netterimages.com/artist/perkins.htm>

# VIDEO CONTENTS

- 3-1 Sagittal Brain
- 3-2 Axial DT Imaging with Color Depiction of Pathways
- 6-1 Axial Sections with Surface Anatomy
- 6-2 Brain: High-Resolution Axial T2
- 7-1 Circle of Willis: Left to Right
- 7-2 Circle of Willis: Head to Foot
- 7-3 Carotid Artery: Left to Right
- 7-4 Carotid Artery: Head to Foot
- 7-5 Brain: Magnetic Resonance Venogram, Left to Right
- 7-6 Brain: Magnetic Resonance Venogram, Head to Foot
- 13-1 Axial Brain
- 13-2 Coronal Brain
- 13-3 Brain: Axial from Axial, Rotation Left to Right
- 13-4 Brain: Sagittal from Sagittal, Rotation Left to Right



# Section I **OVERVIEW OF THE NERVOUS SYSTEM**



## **1. Neurons and Their Properties**

Anatomical and Molecular Properties

Electrical Properties

Neurotransmitter and Signaling Properties

## **2. Skull and Meninges**

## **3. Brain**

## **4. Brain Stem and Cerebellum**

## **5. Spinal Cord**

## **6. Ventricles and the Cerebrospinal Fluid**

## **7. Vasculature**

Arterial System

Venous System

## **8. Developmental Neuroscience**

# 1

## NEURONS AND THEIR PROPERTIES

### Anatomical and Molecular Properties

- 1.1 Neuronal Structure
- 1.2 3D Neuronal Structure and Neurohistology
- 1.3 Types of Synapses
- 1.4 Neuronal Cell Types
- 1.5 Glial Cell Types
- 1.6 Astrocyte Biology
- 1.7 Microglial Biology
- 1.8 Oligodendrocyte Biology
- 1.9 Neuronal Growth Factors and Trophic Factors
- 1.10 Stem Cells in the CNS: Intrinsic and Extrinsic Mechanisms
- 1.11 Stem Cell Therapy
- 1.12 Blood-Brain Barrier
- 1.13 Inflammation in the CNS
- 1.14 Axonal Transport in the CNS and PNS
- 1.15 Myelination of CNS and PNS Axons
- 1.16 Development of Myelination and Axon Ensheathment

### Electrical Properties

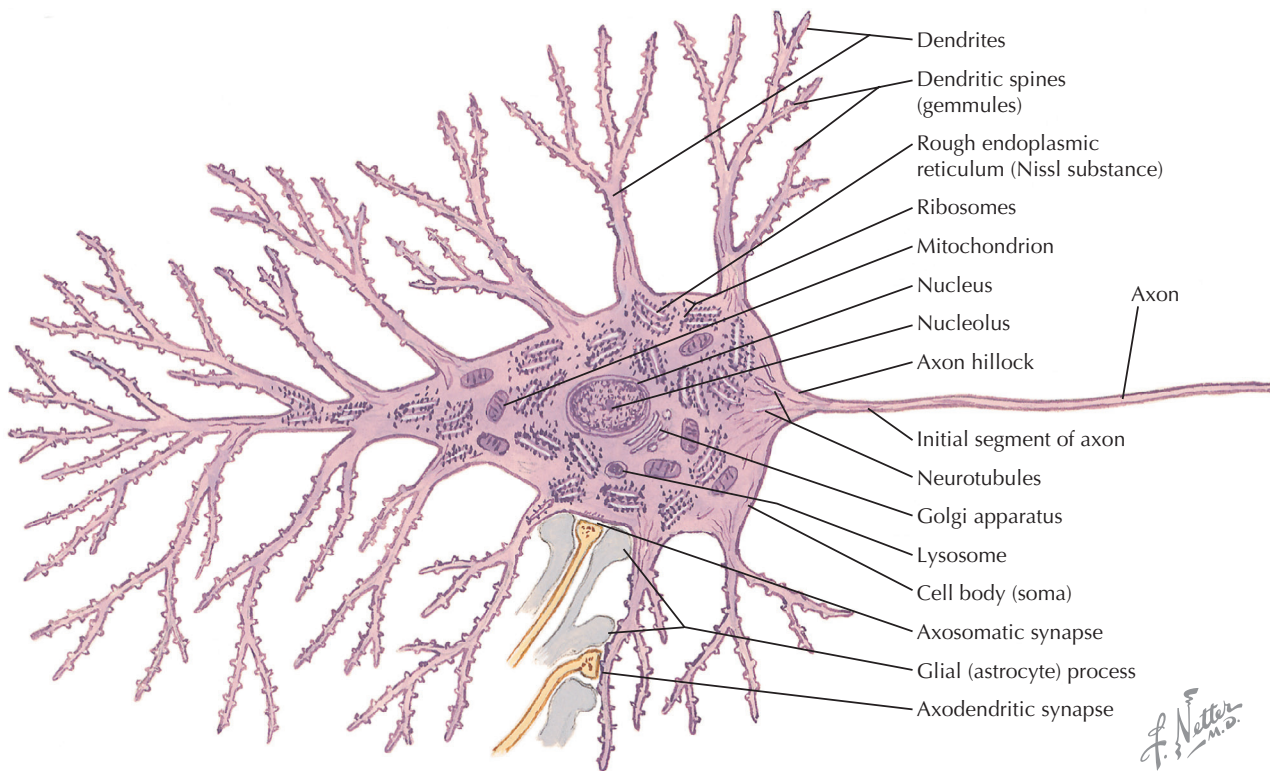
- 1.17 Neuronal Resting Potential
- 1.18 Neuronal Membrane Potential and Sodium Channels
- 1.19 Graded Potentials in Neurons
- 1.20 Mechanisms of Excitatory Postsynaptic Potentials and Inhibitory Postsynaptic Potentials
- 1.21 Action Potentials

- 1.22 Propagation of the Action Potential
- 1.23 Conduction Velocity
- 1.24 Classification of Peripheral Nerve Fibers by Size and Conduction Velocity
- 1.25 Electromyography and Conduction Velocity Studies
- 1.26 Presynaptic and Postsynaptic Inhibition
- 1.27 Spatial and Temporal Summation
- 1.28 Normal Electrical Firing Patterns of Cortical Neurons and the Origin and Spread of Seizures
- 1.29 Electroencephalography
- 1.30 Types of Electrical Discharges in Generalized Seizures and Sites of Action of Antiseizure Medications
- 1.31 Visual and Auditory Evoked Potentials

### Neurotransmitter and Signaling Properties

- 1.32 Synaptic Morphology
- 1.33 Mechanisms of Molecular Signaling in Neurons
- 1.34 Neurotransmitter Release
- 1.35 Multiple Neurotransmitter Synthesis, Release, and Signaling from Individual Neurons
- 1.36 Neuronal Signal Transduction: Local Regulation of Synaptic Strength at an Excitatory Synapse
- 1.37 Neuronal Signal Transduction: Regulation of Nuclear Signaling
- 1.38 Glucocorticoid Regulation of Neurons and Apoptosis
- 1.39 Chemical Neurotransmission





## ANATOMICAL AND MOLECULAR PROPERTIES

### 1.1 NEURONAL STRUCTURE

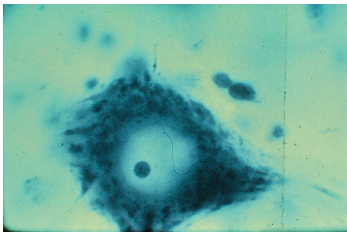
Neuronal structure reflects the functional characteristics of the individual neuron. Incoming information is projected to a neuron mainly through axonal terminations on the cell body and dendrites. These synapses are isolated and are protected by astrocytic processes. The dendrites usually make up the greatest surface area of the neuron. Some protrusions from dendritic branches (dendritic spines) are sites of specific axodendritic synapses. Each specific neuronal type has a characteristic dendritic branching pattern called the dendritic tree, or dendritic arborizations. The neuronal cell body varies from a few micrometers ( $\mu\text{m}$ ) in diameter to more than  $100\ \mu\text{m}$ . The neuronal cytoplasm contains extensive rough endoplasmic reticulum (rough ER), reflecting the massive amount of protein synthesis necessary to maintain the neuron and its processes. The Golgi apparatus is involved in packaging potential signal molecules for transport and release. Large numbers of mitochondria are necessary to meet the huge energy demands of neurons, particularly those related to the maintenance of ion pumps and membrane potentials. Each neuron has a single (or occasionally no) axon, usually emerging from the cell body or occasionally from a dendrite (e.g., some hippocampal CA neurons). The cell body tapers to the axon at the axon hillock, followed by the initial segment of the axon, which contains the  $\text{Na}^+$  channels, the first site where action potentials are initiated. The axon extends for a variable distance from the cell body (up to 1 m or more). An axon larger than 1 to  $2\ \mu\text{m}$  in diameter is insulated by a sheath of myelin provided by oligodendroglia in the central nervous system (CNS) or Schwann cells in the peripheral nervous system (PNS). An axon may branch into more than 500,000 axon terminals, and may terminate in a highly localized and cir-

cumscribed zone (e.g., primary somatosensory axon projections used for fine discriminative touch) or may branch to many disparate regions of the brain (e.g., noradrenergic axonal projections of the locus coeruleus). A neuron whose axon terminates at a distance from its cell body and dendritic tree is called a macroneuron or a Golgi type I neuron; a neuron whose axon terminates locally, close to its cell body and dendritic tree, is called a microneuron, a Golgi type II neuron, a local circuit neuron, or an interneuron. There is no typical neuron because each type of neuron has its own specialization. However, pyramidal cells and lower motor neurons are commonly used to portray a so-called typical neuron.

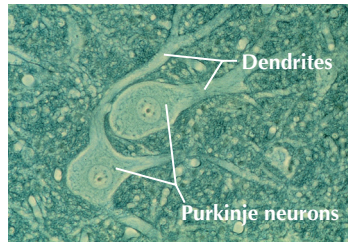
### CLINICAL POINT

Neurons require extraordinary metabolic resources to sustain their functional integrity, particularly that related to the maintenance of membrane potentials for the initiation and propagation of action potentials. Neurons require aerobic metabolism for the generation of adenosine triphosphate (ATP) and have virtually no ATP reserve, so they require continuous delivery of glucose and oxygen, generally in the range of 15% to 20% of the body's resources, which is a disproportionate consumption of resources. During starvation, when glucose availability is limited, the brain can shift gradually to using beta-hydroxybutyrate and acetoacetate as energy sources for neuronal metabolism; however, this is not an instant process and is not available to buffer acute hypoglycemic episodes. An ischemic episode of even 5 minutes, resulting from a heart attack or an ischemic stroke, can lead to permanent damage in some neuronal populations such as pyramidal cells in the CA1 region of the hippocampus. In cases of longer ischemia, widespread neuronal death can occur. Because neurons are postmitotic cells, except for a small subset of interneurons, dead neurons are not replaced. One additional consequence of the postmitotic state of most neurons is that they are not sources of tumor formation. Brain tumors derive mainly from glial cells, ependymal cells, and meningeal cells.

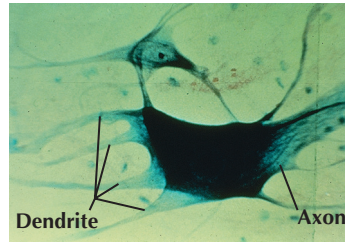




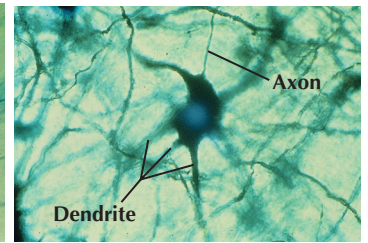
**A.** Spinal cord lower motor neuron. Nissl substance (rough endoplasmic reticulum) stains purple. The nucleolus is stained in the clear nucleus. Cresyl violet stain.



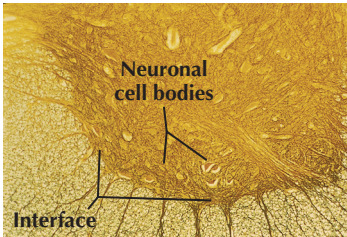
**B.** Cerebellar Purkinje neurons. Large dendrites branch from the cell body. Intraneuronal neurofibrils and background neural processes (neuropil) stain densely. Silver stain.



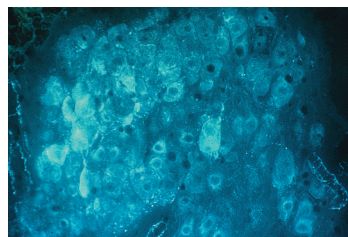
**C.** Spinal cord neuron. Many large dendrites emerge from the cell body, and the smaller axon extends from the large neuron at the 3 o'clock position. Ink stain.



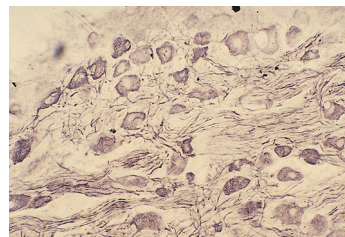
**D.** Reticular formation neuron. Heavy metal impregnation of selective neurons revealing the cell body and all processes. Golgi stain.



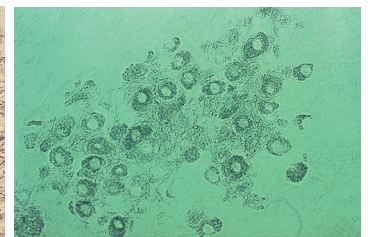
**E.** Spinal cord ventral horn. Neuronal cell bodies and the tangle of axons and dendrites seen in the neuropil of the ventral horn. The interface between gray matter and white matter is conspicuous. Cajal stain.



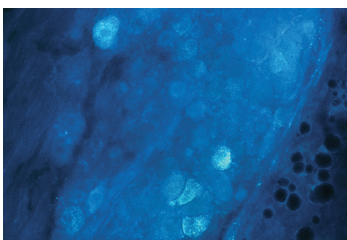
**F.** Superior mesenteric-celiac ganglion. Glyoxylic acid fluorescence histochemistry demonstrating noradrenergic cell bodies.



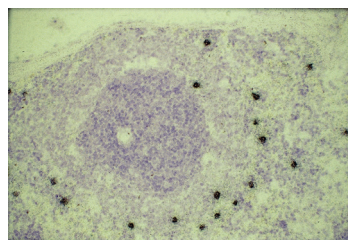
**G.** Superior mesenteric-celiac ganglion. Immunohistochemical stain demonstrating the presence of interleukin-2 receptors in these neurons.



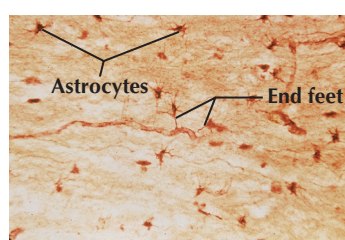
**H.** Superior mesenteric-celiac ganglion. Acetylcholinesterase (AChE) histochemical stain demonstrating the presence of this enzyme, which cleaves acetylcholine to choline and acetyl coenzyme A.



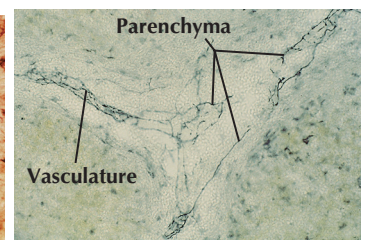
**I.** Neurons in superior mesenteric-celiac ganglion stained with fluorogold, which has been transported retrogradely from an injection site into immune tissue innervated by NA fibers from these NA ganglion cells in a rat.



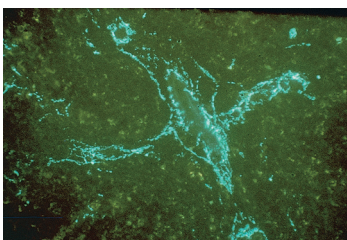
**J.** Immunocytes in the marginal zone of the spleen. In-situ hybridization demonstrating the presence of corticotropin-releasing factor (CRF) gene in these darkly staining nonneuronal cells. CRF is an important releasing factor secreted by neurons into the hypophyseal portal system in the hypothalamus. CRF also is present in, and secreted by, nonneuronal cells in the immune system.



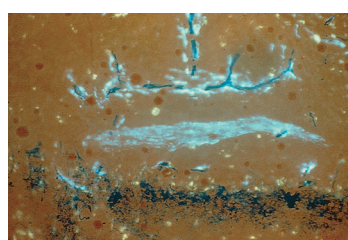
**K.** CNS astrocytes with processes extending into the gray matter and "end feet" extending to the surface of CNS blood vessels with a blood-brain barrier. Silver stain.



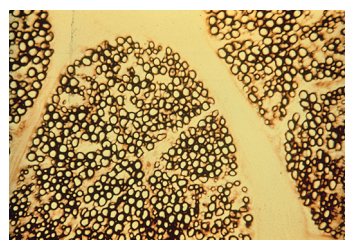
**L.** Axons from NA sympathetic postganglionic neurons innervating the vasculature and parenchyma (T lymphocyte zone and marginal zone) of the spleen. Immunohistochemical stain for tyrosine hydroxylase (TH), the rate-limiting enzyme for the synthesis of catecholamines from tyrosine.



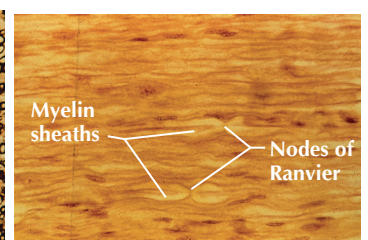
**M.** Same NA axons as in part L. Stained for norepinephrine with glyoxylic acid fluorescence histochemistry.



**N.** Same NA axons as in part M, with added injection of gel ink (dark blue) to demonstrate the vasculature. Gel ink also is picked up by macrophages in the marginal zone.

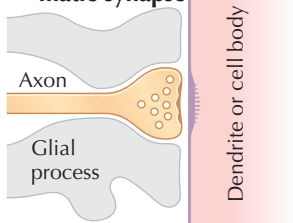
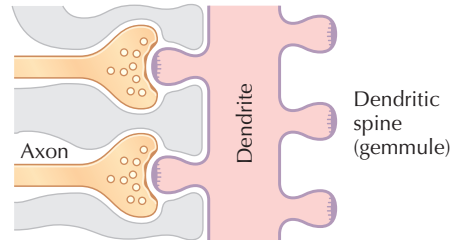
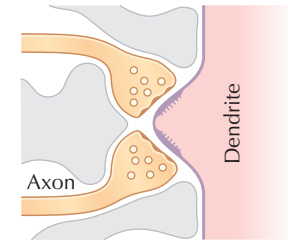
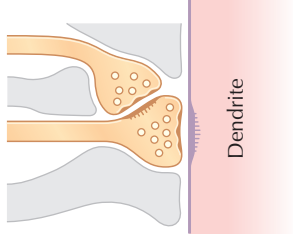
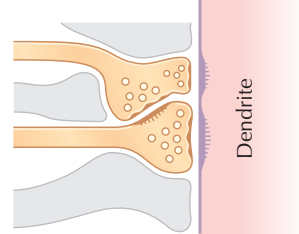
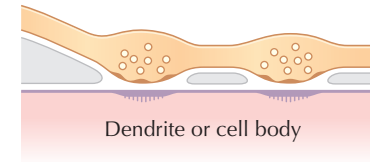
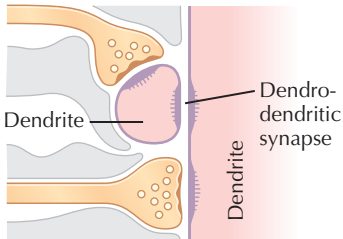
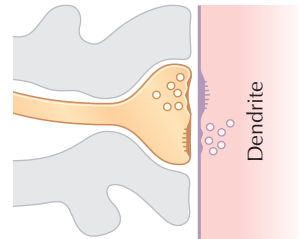
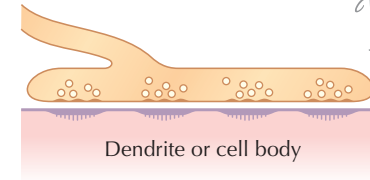


**O.** Myelinated fascicles in a peripheral nerve cut in cross-section. Osmic acid stain reveals myelinated axons but not unmyelinated axons.

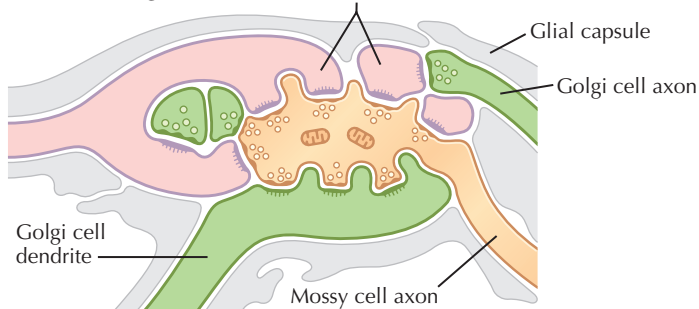
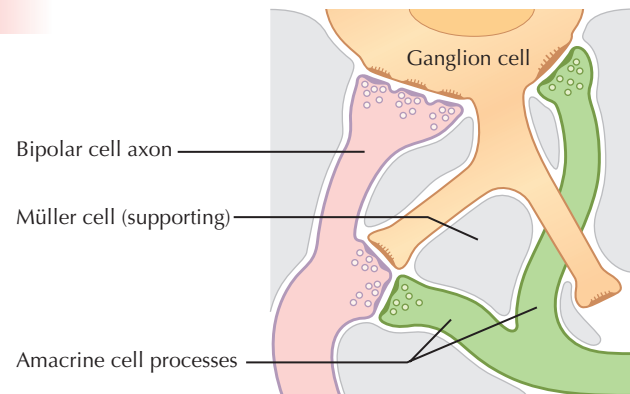


**P.** Axons in a peripheral nerve cut in longitudinal section. Oil red O stain demonstrating longitudinal axons surrounded by myelin sheaths (light-colored areas), with conspicuous appositions of sheaths at nodes of Ranvier.

## 1.2 3D NEURONAL STRUCTURE AND NEUROHISTOLOGY

**A. Simple axodendritic or axosomatic synapse****B. Dendritic spine synapse****C. Dendritic crest synapse****D. Simple synapse plus axoaxonic synapse****E. Combined axoaxonic and axodendritic synapse****F. Varicosities ("boutons en passant")****G. Dendrodendritic synapse****H. Reciprocal synapse****I. Serial synapse**

*F. Netter M.D.*  
with  
**J. Perkins**  
MS, MFA

**J. Cerebellar glomerulus****K. Inner plexiform layer of retina**

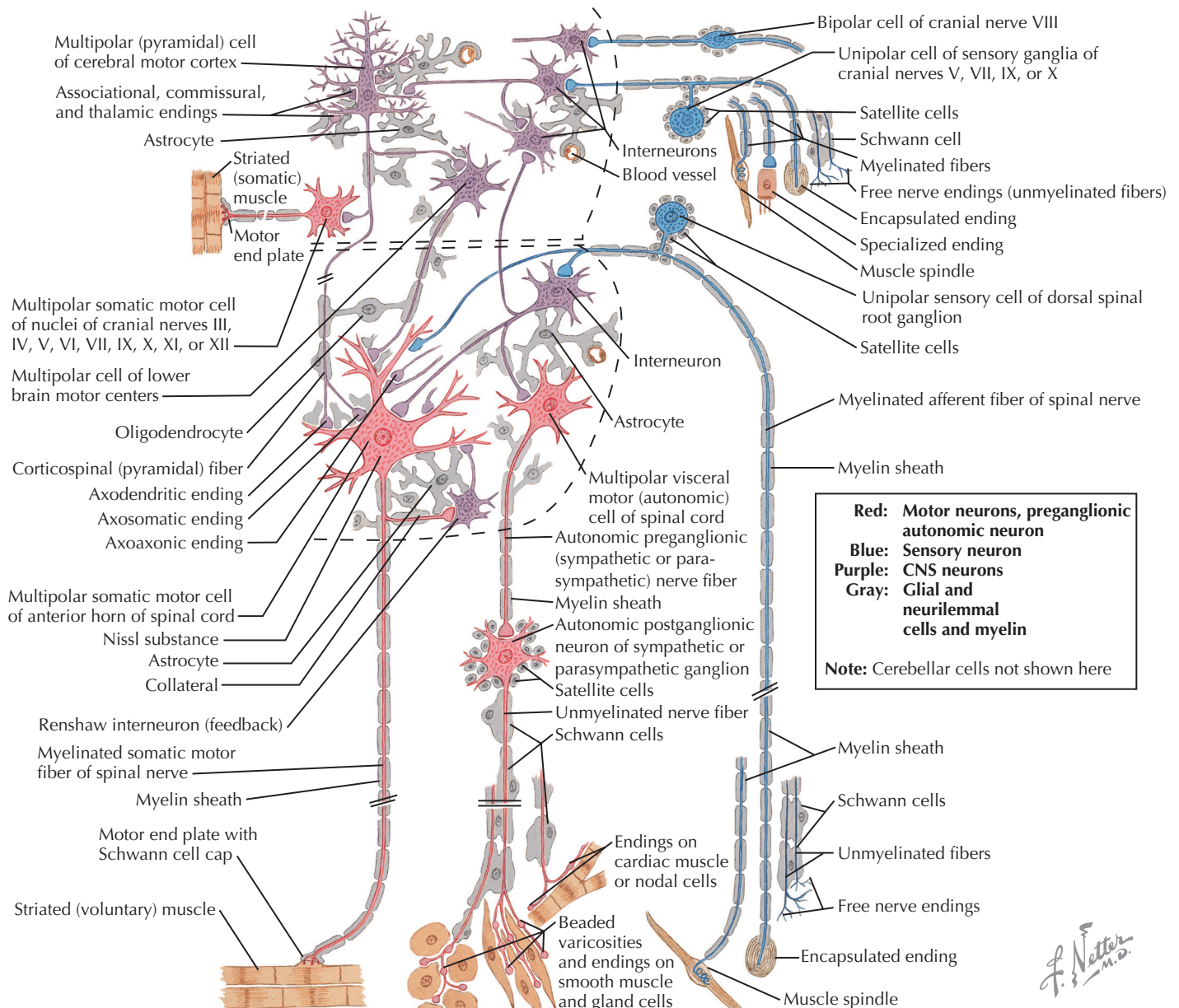
### 1.3 TYPES OF SYNAPSES

A synapse is a site where an arriving action potential, through excitation-secretion coupling involving  $\text{Ca}^{2+}$  influx, triggers the release of one or more neurotransmitters into the synaptic cleft (typically 20  $\mu\text{m}$  across). The neurotransmitter acts on receptors on the target neuronal membrane, altering the membrane potential from its resting state. These postsynaptic potentials are called graded potentials. Most synapses carrying information toward a target neuron terminate as axodendritic or axosomatic synapses. Specialized synapses, such as reciprocal synapses or complex arrays of synaptic interactions, provide specific regulatory control over the excitability of their target neurons. Dendrodendritic synapses aid in the coordinated firing of groups of related neurons such as the phrenic nucleus neurons that cause contraction of the diaphragm.

#### CLINICAL POINT

The configurations of the synapses of key neuronal populations in particular regions of the brain and of target cells in the periphery determine the relative influence of that input. At the neuromuscular junction, a sufficient amount of acetylcholine is usually released by an action potential in the motor axon to guarantee that the muscle end plate potential reaches threshold and initiates an action potential. In contrast, the neuronal inputs into reticular formation neurons and many other types of neurons require either temporal or spatial summation to allow the target neuron to reach threshold; this orchestration involves coordinated multisynaptic regulation. In some key neurons such as lower motor neurons (LMNs), input from brain stem upper motor neurons (UMNs) is directed mainly through spinal cord interneurons and requires extensive summation to activate the LMNs; in contrast, direct monosynaptic corticospinal UMNs input onto some LMNs, such as those regulating fine finger movements, terminate close to the axon hillock/initial segment; and can directly initiate an action potential in the LMNs. Some complex arrays of synapses among several neuronal elements, such as those seen in structures such as the cerebellum and retina, permit modulation of key neurons by both serial and parallel arrays of connections, providing lateral modulation of neighboring neuronal excitability.



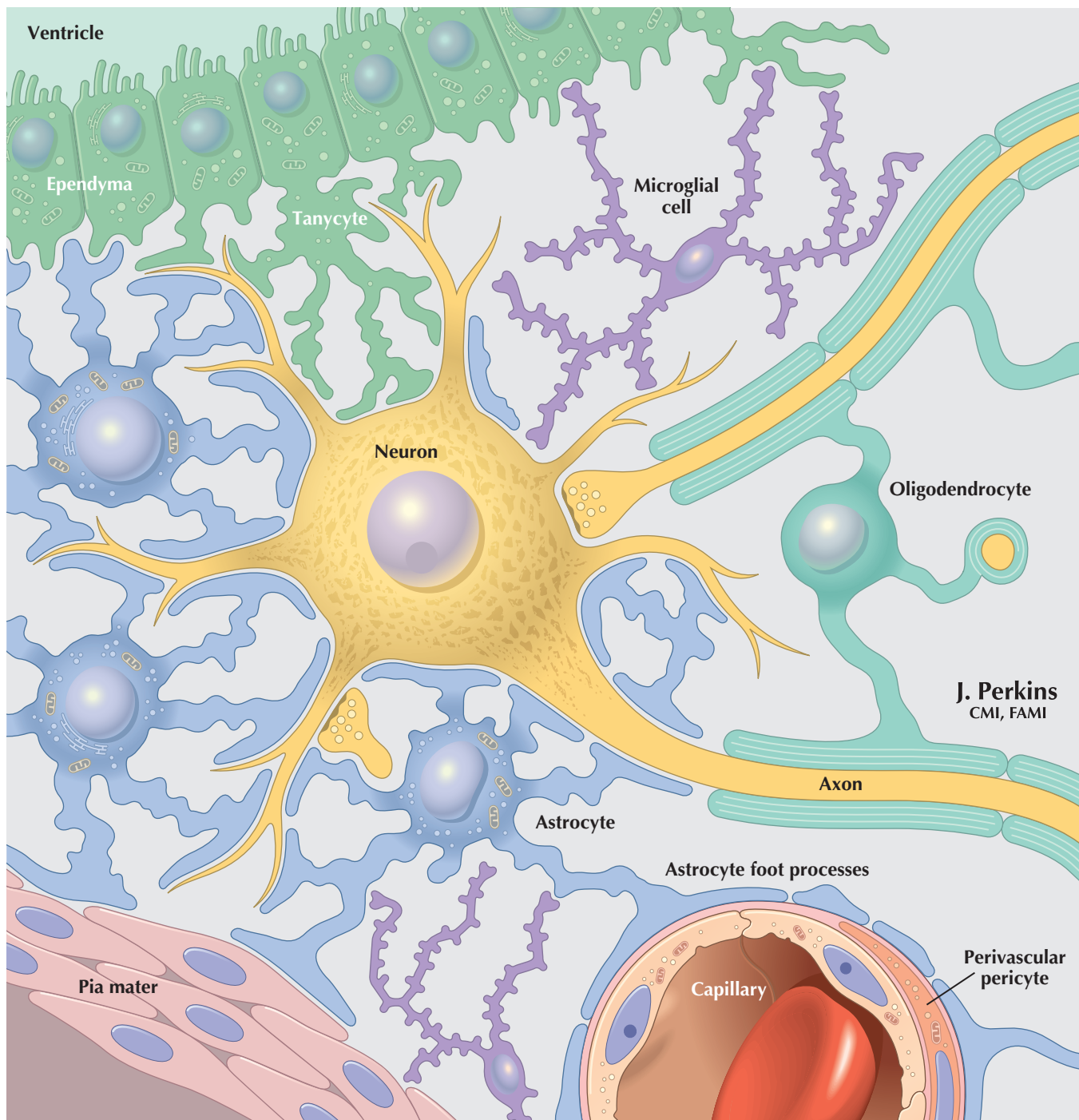


## 1.4 NEURONAL CELL TYPES

Local interneurons and projection neurons demonstrate characteristic size, dendritic arborizations, and axonal projections. In the CNS (denoted by dashed lines), glial cells (astrocytes, microglia, oligodendroglia) provide support, protection, and maintenance of neurons. Schwann cells and satellite cells provide these functions in the PNS. The primary sensory neurons (blue) provide sensory transduction of incoming energy or stimuli into electrical signals that are carried into the CNS. The neuronal outflow from the CNS is motor (red) to skeletal muscle fibers via neuromuscular junctions, or is autonomic preganglionic (red) to autonomic ganglia, whose neurons innervate cardiac muscle, smooth muscle, secretory glands, metabolic cells, or cells of the immune system. Neurons other than primary sensory neurons, LMNs, and preganglionic autonomic neurons are located in the CNS in the brain (enclosed by upper dashed lines) or spinal cord (enclosed by lower dashed lines). Neurons and glia are not drawn to scale.

### CLINICAL POINT

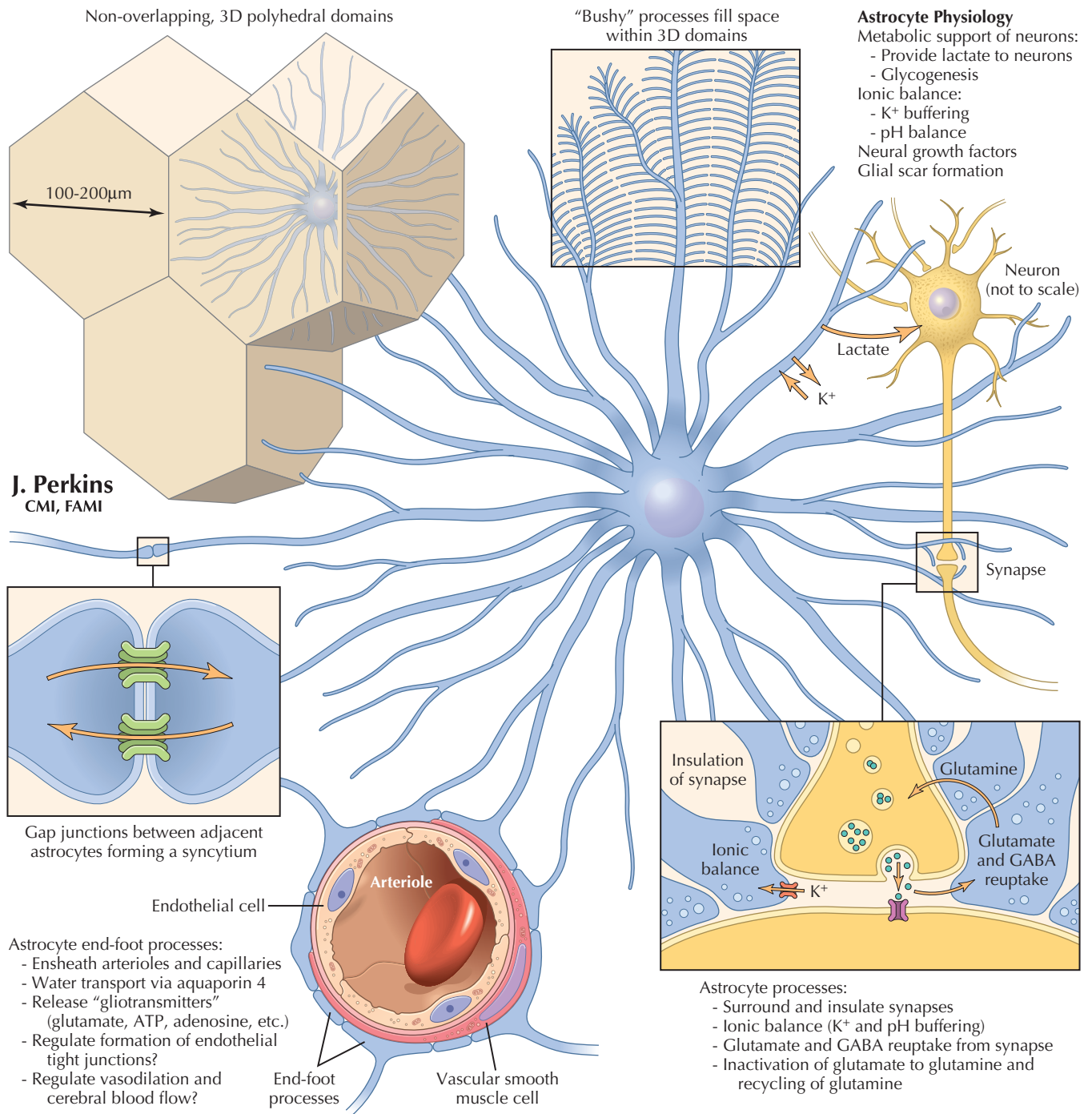
Neuronal form and configuration provide evidence of the role of that particular type of neuron. Dorsal root ganglion cells have virtually no synapses on the cell body; the sensory receptor is contiguous with the initial segment of the axon to permit direct activation of the initial segment upon reaching a threshold stimulus. This arrangement provides virtually no opportunity for centrifugal control of the initial sensory input; rather, control and analysis of the sensory input occurs in the CNS. Purkinje neurons in the cerebellum have huge planar dendritic trees, with activation occurring via hundreds of parallel fibers and the background excitability influenced by climbing fiber control. This type of array allows network modulation of Purkinje cell output, via neurons of the deep cerebellar nuclei, to UMNs, a control mechanism that permits fine-grained, ongoing adjustments to smooth and coordinated motor activities. Small interneurons in many regions have local and specialized functions that have local circuit connections, whereas large isodendritic neurons of the reticular formation receive widespread, polymodal, nonlocal input, which is important for general arousal of the cerebral cortex and consciousness. Damage to these key neurons may result in coma. LMNs and preganglionic autonomic neurons receive tremendous convergence upon their dendrites and cell bodies to orchestrate the final pattern of activation of these final common pathway neurons through which the peripheral effector tissues are signaled and through which all behavior is achieved.



### 1.5 GLIAL CELL TYPES

Astrocytes provide structural isolation of neurons and their synapses and provide ionic ( $K^+$ ) sequestration, trophic support, and support for growth and signaling functions to neurons. Oligodendroglia (oligodendrocytes) provide myelination of axons in the CNS. Microglia are scavenger cells that participate in phagocytosis, inflammatory responses, cytokine

and growth factor secretion, and some immune reactivity in the CNS. Perivascular cells participate in similar activities at sites near the blood vessels. Schwann cells provide myelination, ensheathment, trophic support, and actions that contribute to the growth and repair of peripheral neurons. Activated T lymphocytes normally can enter and traverse the CNS for immune surveillance for a period of approximately 24 hours.



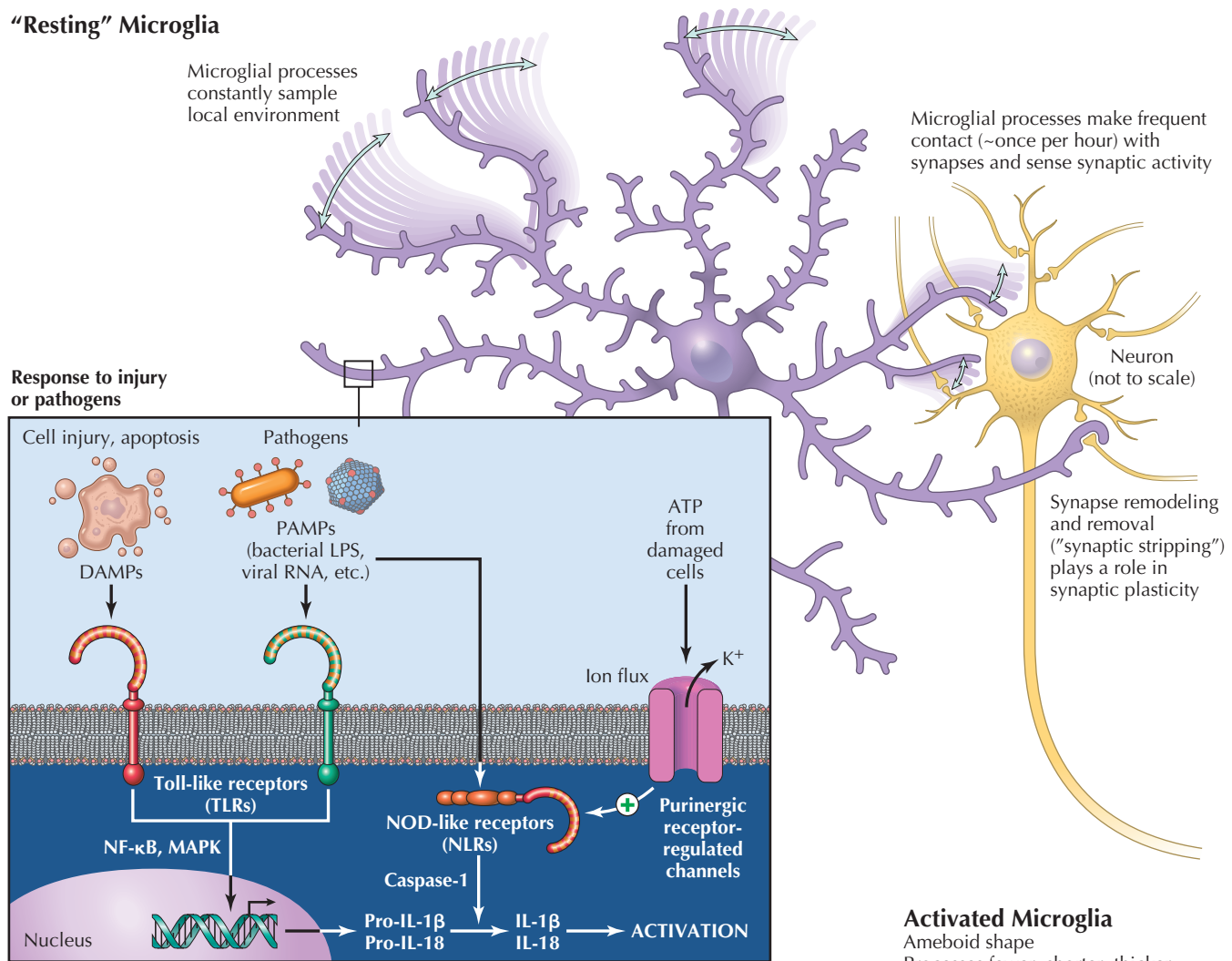
## 1.6 ASTROCYTE BIOLOGY

Astrocytes are the most abundant glial cells in the CNS. They arise from neuroectoderm and are intimately associated with neural processes, synapses, vasculature, and the pial-glial membrane investing the CNS. Astrocytes in gray matter are called *protoplasmic astrocytes*, and in white matter they are called *fibrous astrocytes*. The somas vary in diameter from a few  $\mu$ m to 10 or more  $\mu$ m. Astrocytes are arrayed in non-overlapping 3D polyhedral domains of 100-200  $\mu$ m across (up to 400  $\mu$ m in hominids). Structurally, astrocytic processes interdigitate, forming a syncytium to protect synapses (as close as 1 $\mu$ m to these structures). Astrocytic endfeet associate

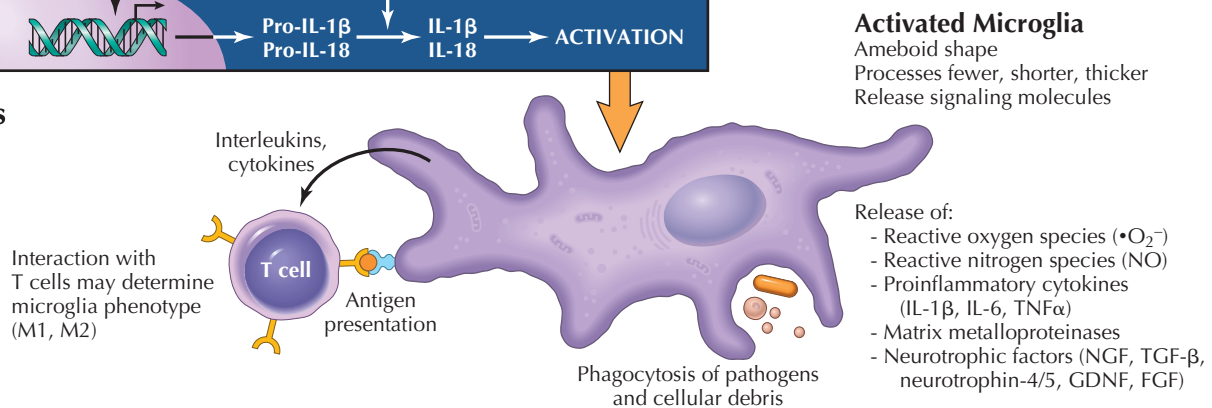
with vascular endothelial cells and associated smooth muscle cells. Astrocytic processes invest the entire pial membrane from the inside.

Physiologically, astrocytic processes affect ion balance (sequester  $K^+$ ), transport water via aquaporin 4 channels, uptake and recycle glutamate and GABA, provide metabolic support to neurons, and can become reactive after CNS injury and lay down glial scar tissue. Astrocytes also can release growth factors and bioactive molecules (termed *gliotransmitters*) such as glutamate, ATP, and adenosine. In development, specialized astrocytes, called *radial glia*, provide a scaffold for orderly neural migrations in the CNS.



**"Resting" Microglia**

**J. Perkins**  
CMI, FAMI

**1.7 MICROGLIAL BIOLOGY**

Microglial cells are mesenchymal cells derived from yolk sac that come to reside in the CNS. They are a unique resident population with the capacity for self-renewal. Microglia provide constant surveillance of the local microenvironment, moving back and forth up to 1.5  $\mu$ m/min. Microglial processes can grow and shrink up to 2-3  $\mu$ m/min. They have a territory 15-30  $\mu$ m wide, with little overlap with each other. Resting microglia have soma of 5-6  $\mu$ m diameter, and activated microglia are ameboid in appearance, with soma of approximately 10  $\mu$ m diameter.

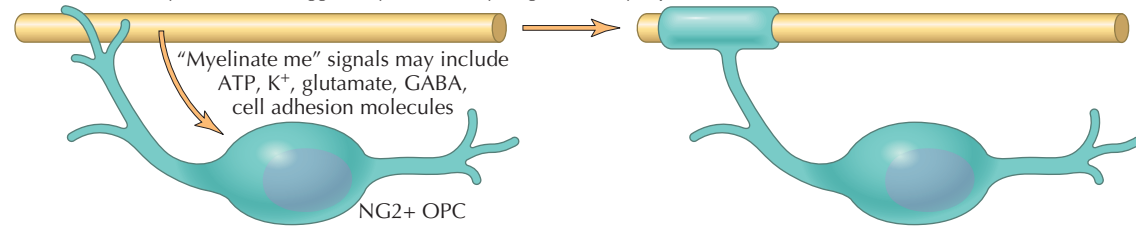
Microglia can carry out phagocytosis of debris and apoptotic cells, remodel and remove synapses in developing and adult CNS, and respond to injury or pathogens. Microglia

have receptors for multiple types of stimuli, such as ATP (indicator of local damage), toll-like receptors (TLRs) that respond to molecules released from dying cells (DAMPs: damage-associated molecular patterns) or pathogens (PAMPs: pathogen associated molecular patterns) such as LPS on gram-negative bacteria, or double-stranded RNA in viruses.

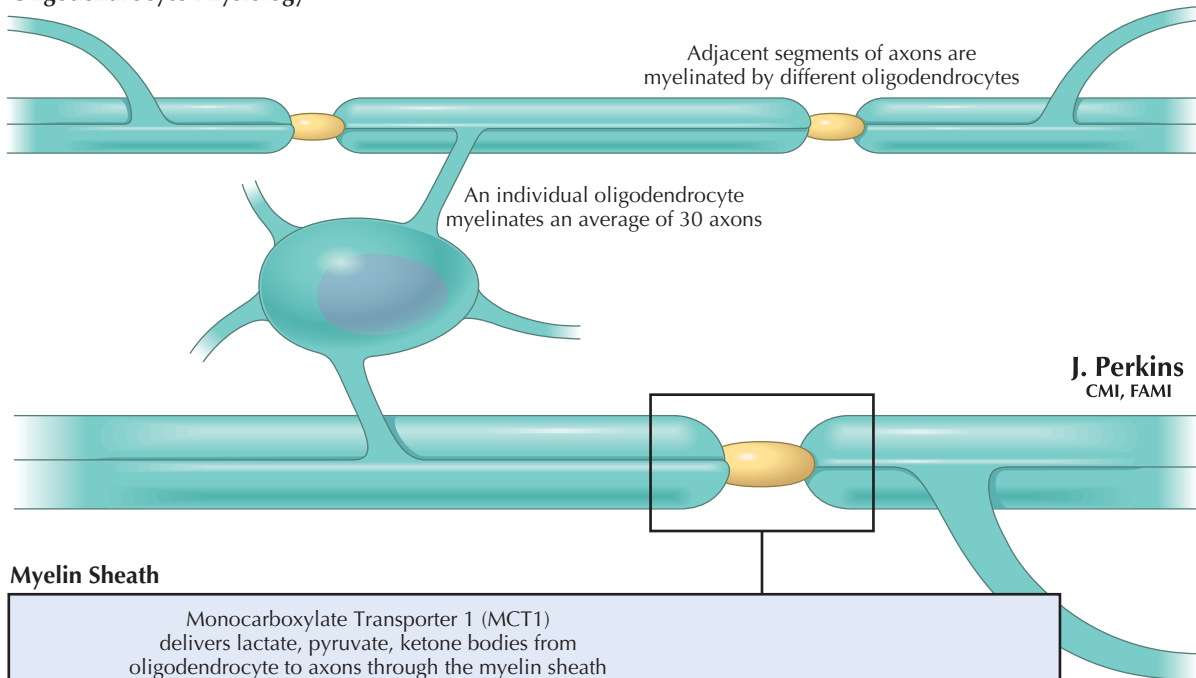
Reactive microglia produce reactive oxygen species (ROS), reactive nitrogen species (RNS, such as NO), proinflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), matrix metalloproteinases (MMPs), and neurotrophic factors (such as NGF, TGF- $\beta$ , neurotrophin 4/5, GDNF, FGF). Such signal molecules from activated microglia can affect neurons and astrocytes, inducing dysfunction.

### Oligodendrocyte Maturation

Functional activity in neurons triggers myelination by oligodendrocyte precursor cells (OPCs)

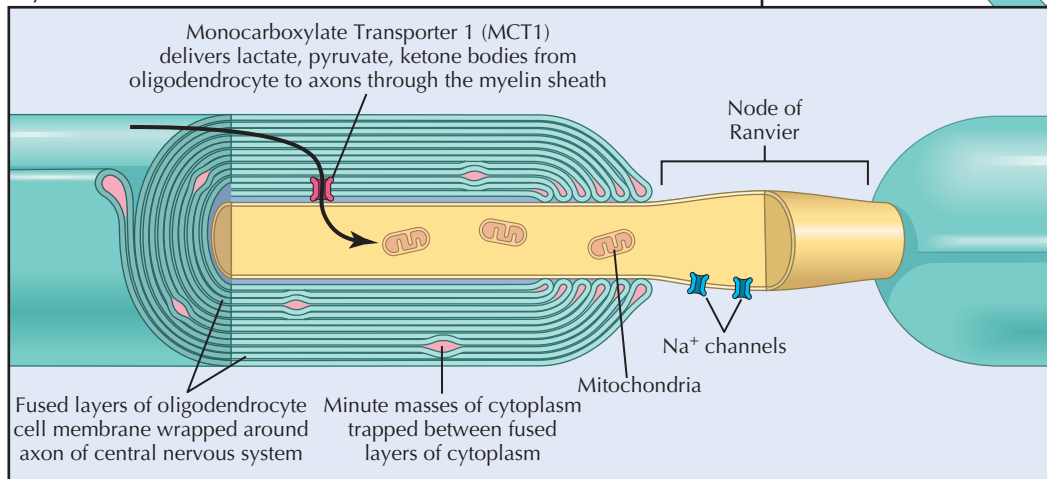


### Oligodendrocyte Physiology



J. Perkins  
CMI, FAMI

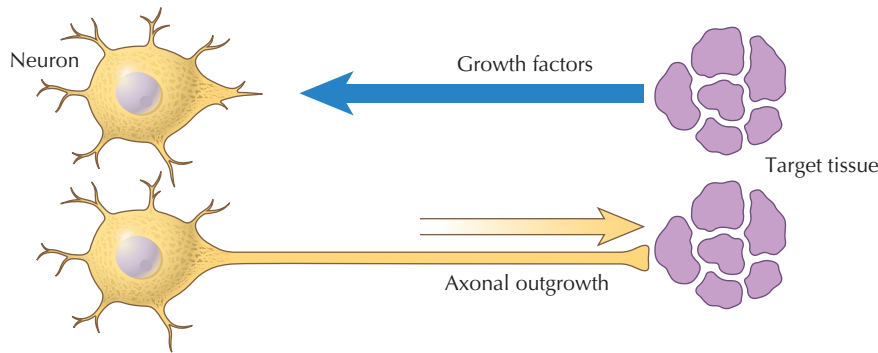
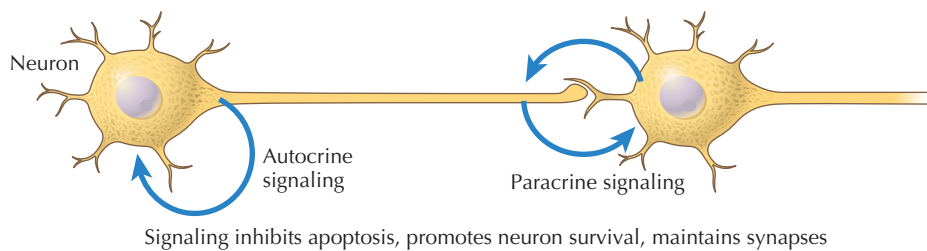
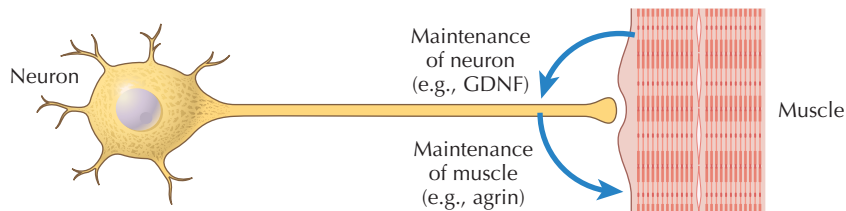
### Myelin Sheath



## 1.8 OLIGODENDROCYTE BIOLOGY

Oligodendrocytes are neuroectodermally derived glial cells that have the major role of myelinating central axons. The trigger for myelination may include associated axonal size and signal molecules (such as ATP, K<sup>+</sup>, glutamate, GABA, and some cell adhesion molecules). Each oligodendrocyte can myelinate individual internodal segments of an average of 30 separate axons (as high as 60 axons); adjacent internodal segments are myelinated by different oligodendrocytes. This pattern of central myelination leaves periodic nodes of Ranvier bare, with sodium channels, at which action potentials (APs) are

reinitiated as they travel down the myelinated axon and its branches (called *saltatory conduction*). Oligodendrocytes can be attacked by antibodies directed at specific oligodendrocyte proteins in multiple sclerosis, leading to oligodendrocyte death and axonal dysfunction. Oligodendrocyte precursor cells can replicate following such insults and remyelinate the denuded central axon segments. Oligodendrocyte membranes possess monocarboxylate transporter 1 (MCT 1), which can deliver lactate, pyruvate, and ketone bodies to the axon. Oligodendrocyte precursor cells (OPCs) are present in the adult CNS and have NG2 and PDGF $\alpha$  receptors.

**I. Growth (e.g., neuronal differentiation, axonal outgrowth)****II. Autocrine and paracrine signaling between and among neurons****III. Reciprocal signaling (e.g., neuromuscular junction)**

**J. Perkins**  
CMI, FAMI

Growth Factor	Source	Receptor	Critical for:
NGF	Skin, hippocampus?	TrkA, p75	Cutaneous nociceptive neurons (small DRG neurons) Sympathetic neurons Basal Forebrain Cholinergic neurons (not the only factor required)
BDNF	Many sites	TrkB, p75	Synaptic plasticity In periphery, BDNF KO mice show loss of vestibular ganglion neurons
NT3	Golgi tendon organs and muscle spindles	TrkC, p75	Loss of proprioceptive sensory neurons in DRG No gamma motoneurons; mice die at birth
NT4	Multiple sites	TrkB, p75	No robust phenotype
GDNF	Muscle	Grfa1, Ret	Partial loss of muscles
CNTF	Muscle?	CNTFRα, gp130	KO of CNTFRα partial loss of muscles, but CNTF KO no loss due to LIF working
IGF-1	Muscle	IGFR-1, IGFR-2	Partial loss of muscles
VEGF	Muscle	Flk-1, Flt-1, Flt-4	Embryonic lethal (required for angiogenesis)

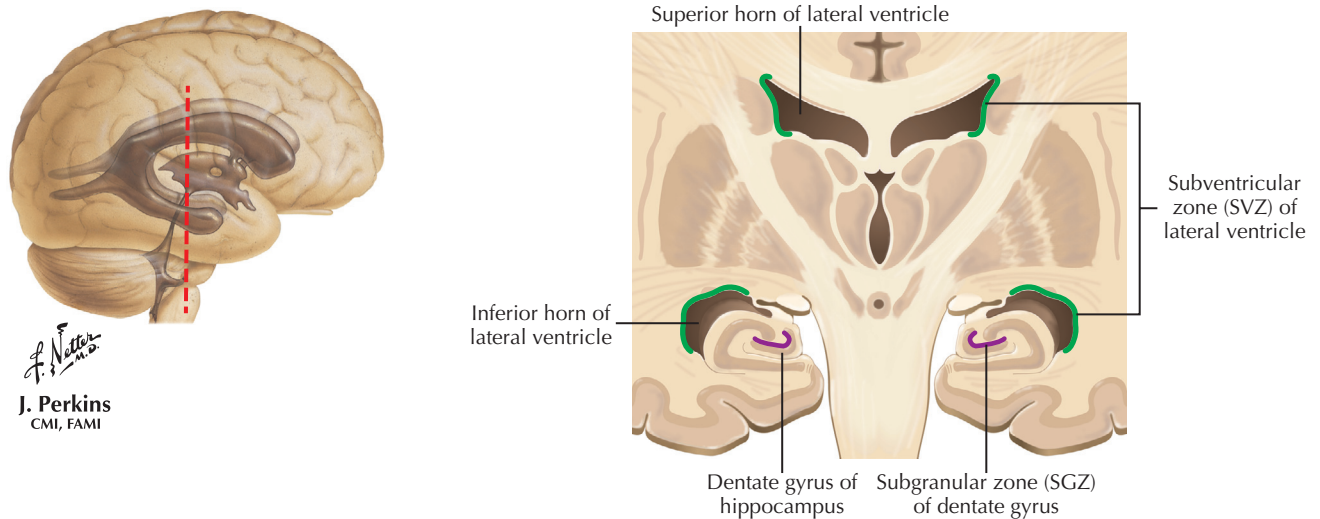
NGF, nerve growth factor; BDNF, brain derived neurotrophic factor; NT3 and NT4, neurotrophic 3 and 4; GDNF, glial cell-line derived neurotrophic factor; CNTF, ciliary neurotrophic factor; IGF-1, insulin-like growth factor 1; VEGF, vascular endothelial growth factor; Trk, tyrosine kinase; KO, knock out; LIF, leukemia inhibitory factor

**1.9 NEURONAL GROWTH FACTORS AND TROPHIC FACTORS**

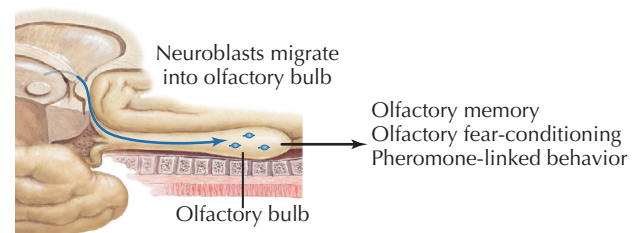
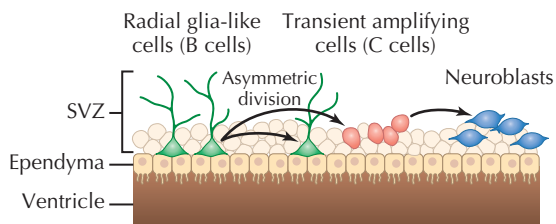
Neuronal growth factors and trophic factors are signal molecules produced by neurons, glia, and target tissues that can influence neuronal differentiation, growth of neurites, establishment of contacts for signaling, maintenance of neural contacts with their central or peripheral targets, and other

functions. These factors act through specific receptors and can induce the production of specific molecules, such as agrin for the maintenance of nicotinic cholinergic receptors at the neuromuscular junction. Several identified growth factors, along with their sourced receptors and possible roles, are provided in the table above.

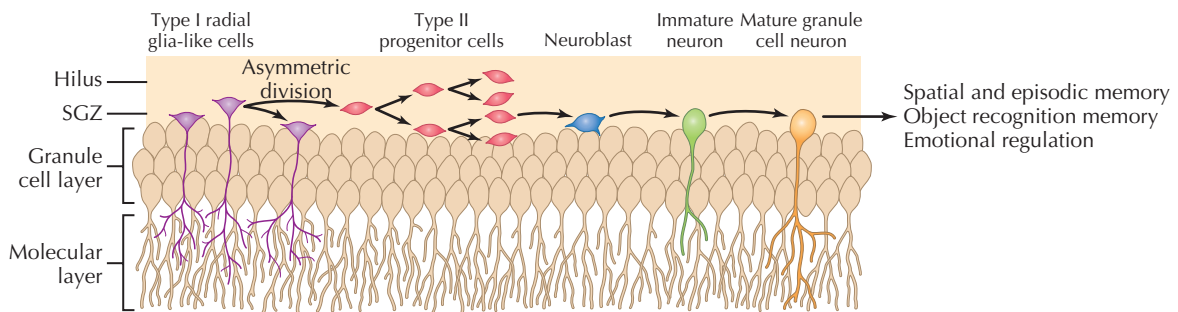




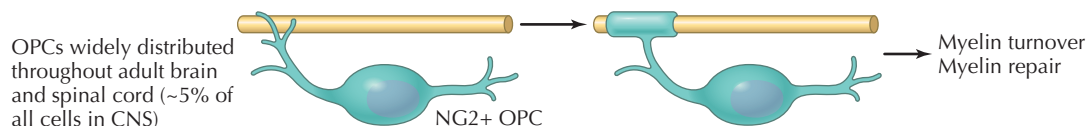
### I. Subventricular zone (SVZ) of lateral ventricle



### II. Subgranular zone (SGZ) of dentate gyrus



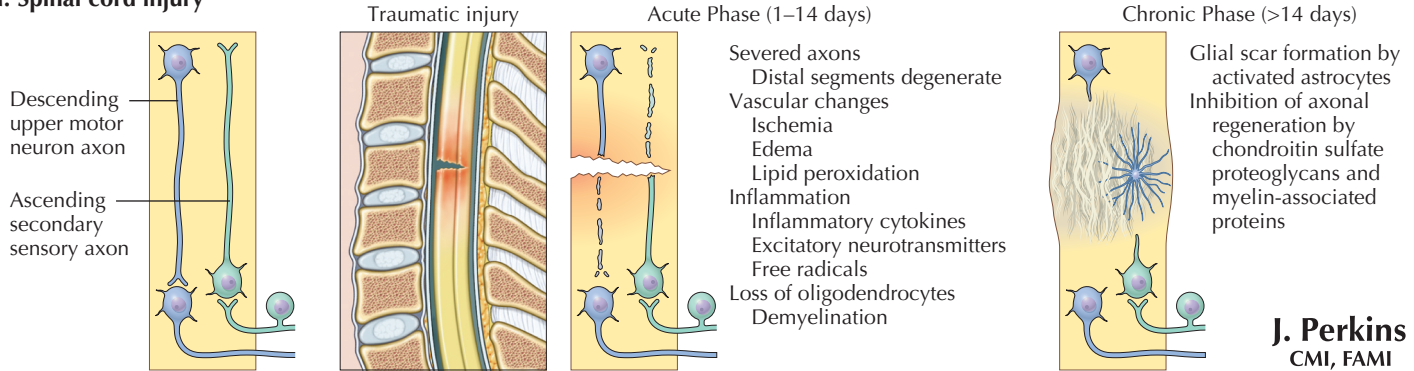
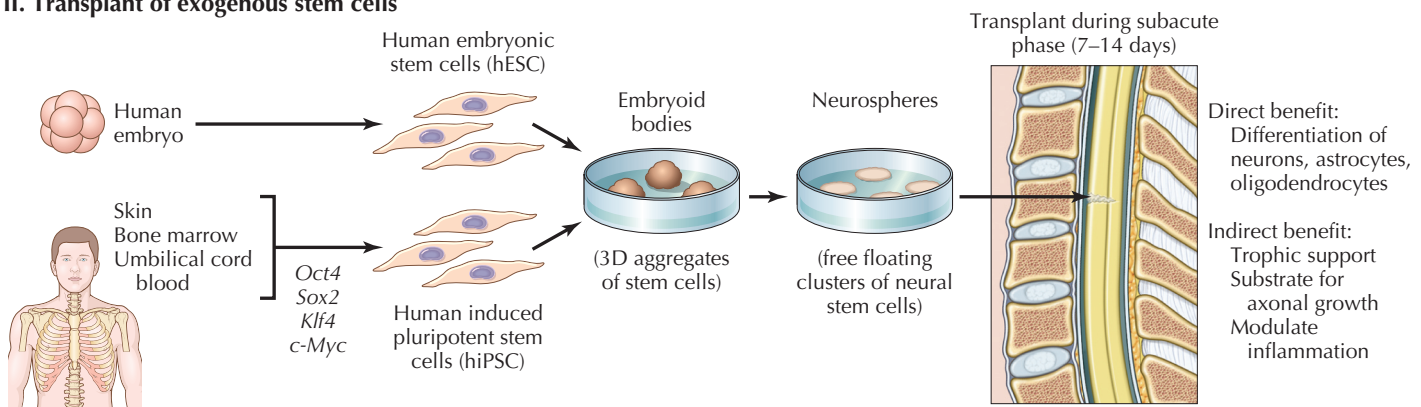
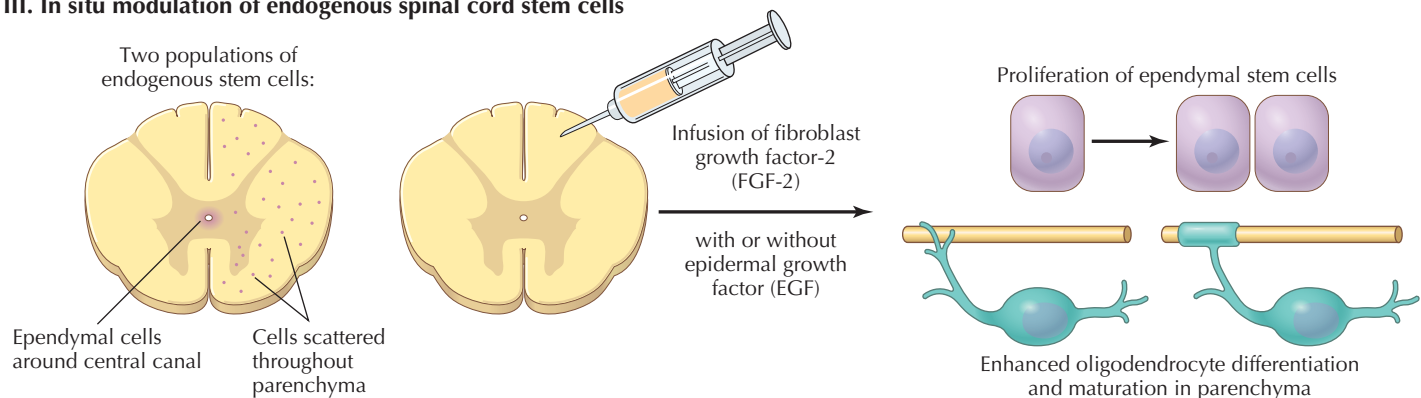
### III. Oligodendrocyte progenitor cells (OPCs)



## 1.10 STEM CELLS IN THE CNS: INTRINSIC AND EXTRINSIC MECHANISMS

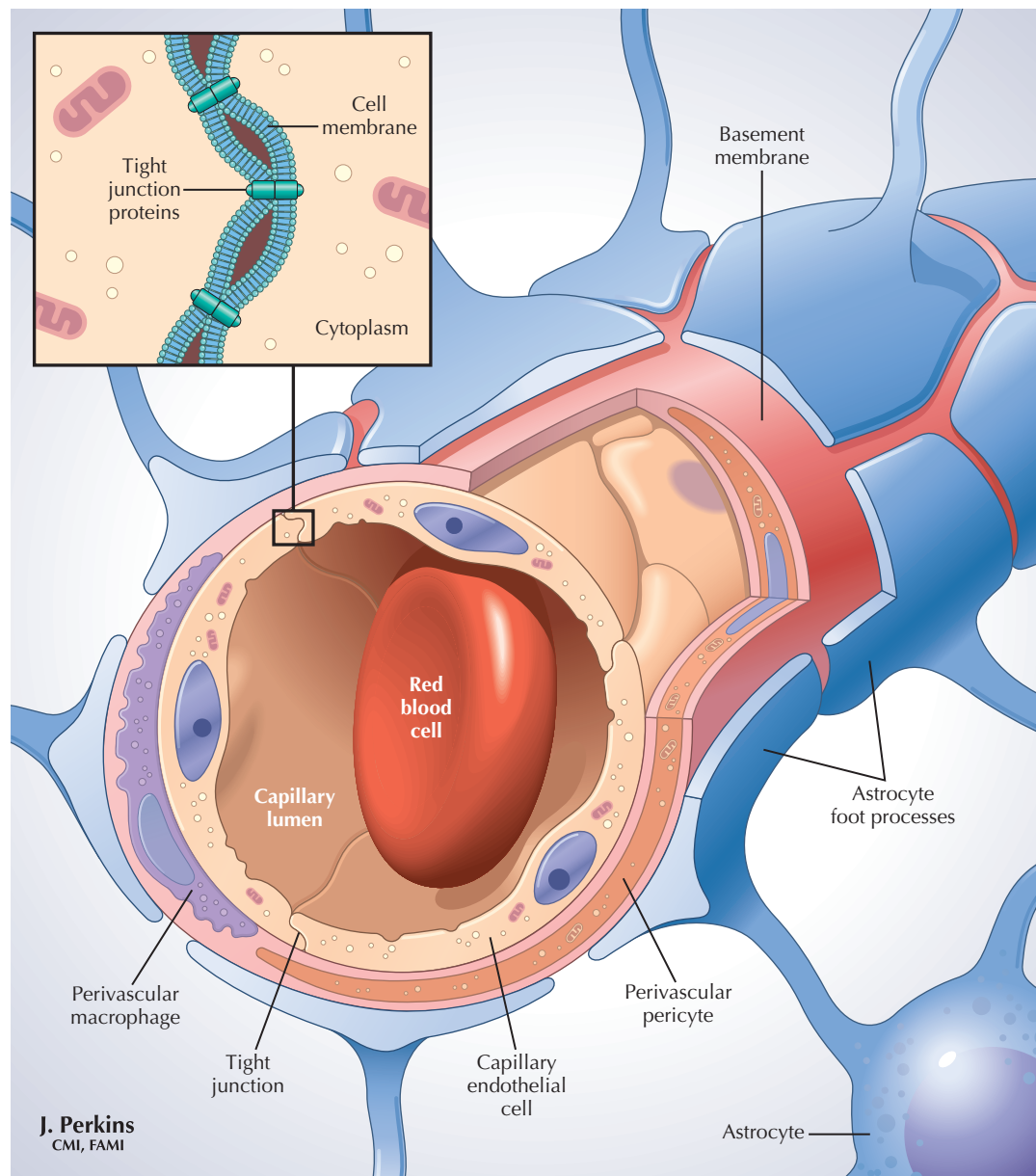
Embryogenesis involves the proliferation of stem cells, followed by differentiation and migration of the resultant cell types. In the CNS, derived from the neural tube, neuronal stem cells persist in the *subventricular* (or subependymal) zone of the lateral ventricles (I). Waves of neuronal proliferation, differentiation, and migration occur during prenatal CNS development. After birth, stem cells in the subventricular zone continue to proliferate and produce granule cells (neurons)

for many brain regions; this process is driven by postnatal environmental stimuli. Throughout adulthood, in the *subgranular zone* of the dentate gyrus, radial glial-like cells give rise to neuroblasts that contribute new granule cell neurons (II). In addition, *oligodendroglial progenitor cells* throughout the CNS can proliferate and then differentiate into mature oligodendrocytes (III). This process can occur after a demyelinating lesion and helps to remyelinate CNS axons (e.g., after a multiple sclerosis lesion).

**I. Spinal cord injury****II. Transplant of exogenous stem cells****III. In situ modulation of endogenous spinal cord stem cells****1.11 STEM CELL THERAPY**

Recent approaches to stem cell therapy after a spinal cord injury are depicted here. *I. The pathologic process of spinal cord injury* shows acute and chronic responses. *II. Use of exogenous stem cells* transplanted during the subacute phase leads to differentiation of neurons and glia and trophic support and

modulation of inflammation. *III. In situ modulation of endogenous stem cells* uses infusion of growth factors. These approaches remain experimental but offer possible applications of knowledge derived from stem cell biology to treat devastating conditions such as spinal cord injury.



### 1.12 BLOOD-BRAIN BARRIER

The blood-brain barrier (BBB) is the cellular interface between the blood and the CNS. It serves to protect the brain from unwanted intrusion by many large molecules and potentially toxic substances and to maintain the interstitial fluid environment to ensure optimal functioning of the neurons and their associated glial cells. The major cellular basis for the BBB consists of the capillary endothelial cells which have an elaborate network of tight junctions; these tight junctions restrict access by many large molecules, including many drugs, to the CNS. Endothelial cells in the CNS also exhibit a low level of pinocytotic activity across the cell, providing selected specific carrier systems for the transport of essential substrates of energy production and amino acid metabolism into the CNS. Astrocytic endfoot processes abut the endothelial cells and their basement membranes; these processes help to transfer important metabolites from the blood to neurons and can influence the expression of some specific gene products in the endothelial cells. These astrocytic processes also can remove excess  $K^+$  and some neurotransmitters from the interstitial fluid.

#### CLINICAL POINT

The BBB, anatomically consisting mainly of the capillary tight junctions of the vascular endothelial cells, serves to protect the CNS from the intrusion of large molecules and potentially damaging agents from the peripheral circulation. The neurons need protection of their ionic and metabolic environment, which is aided by glial cells and the BBB. There are selected areas (windows on the brain) where the BBB is not present, such as the median eminence, the area postrema, the organum vasculosum of the lamina terminalis, and others, and where specialized cells can sample the peripheral circulation and can initiate corrective brain mechanisms to protect the neuronal environment. The presence of the BBB presents a challenge for pharmacotherapy aimed at the CNS; many antibiotics and other agents will not penetrate the BBB and must be coupled to a carrier molecule that does cross or must be injected intrathecally. In some pathological circumstances, such as the presence of a brain tumor, neuronal degeneration resulting from a neurodegenerative disease, the presence of a high concentration of a solute, or a stroke, the BBB is disrupted extensively, exposing the internal CNS milieu to molecules in the peripheral circulation. Therapeutic strategies now are being tested that will achieve transport of desired pharmacotherapeutic agents across the BBB and will protect the brain from unwanted disruption of the BBB in pathological circumstances.

**I. Response to intrinsic damage (acute stroke, trauma, bacterial infection, etc.)****A. Rapid inflammatory response**

Tissue damage  
DAMPs  
PAMPs  
Pathogens

Activated microglia

Ingestion of pathogens  
and cellular debris

**B. Delayed inflammatory response**

Cytokines,  
chemokines

ROS, RNS

Recruitment of  
peripheral blood  
elements (macrophages, neutrophils, T cells)

**C. Healing**

Breakdown of  
blood-brain  
barrier

Neuronal  
dysfunction  
and loss

Conversion of astrocytes  
from supportive role  
to scar formation

**II. Response to extrinsic stimuli**

Extrinsic inflammatory stimuli  
such as infection and chronic  
disease (e.g., CVD, arthritis)  
acting via:

1. Crossing blood-brain barrier
2. Action on endothelium to  
produce prostaglandins
3. Peripheral stimulation of the  
sensory part of the vagus n.

Activation of local microglia

Recruitment of peripheral  
blood elements

PGE<sub>2</sub>

Cytokines,  
chemokines,  
PGE<sub>2</sub>,  
ROS, RNS

Neuronal dysfunction  
and loss

**Inflammatory Mediators**

Cytokines/chemokines:

IL-1

TNF $\alpha$

CCL2

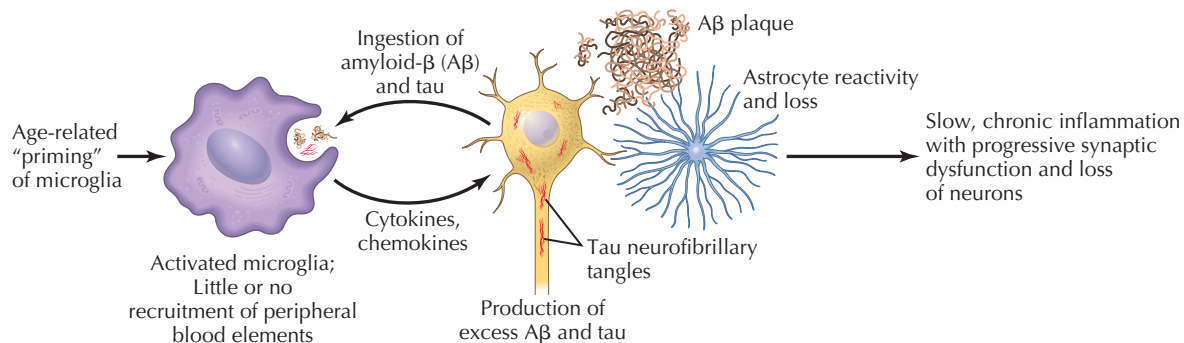
TGF $\beta$

ROS (e.g., superoxide)

RNS (e.g., NO)

Prostaglandins (e.g., PGE<sub>2</sub>)

**J. Perkins**  
CMI, FAMI

**III. Response to intrinsic proteinopathy or neurodegenerative process (e.g., Alzheimer's Disease)****1.13 INFLAMMATION IN THE CNS**

Inflammatory responses in the CNS occur under several different conditions. *I. Inflammatory response to intrinsic damage* such as stroke, trauma, or infection involves an acute inflammatory response, a delayed inflammatory response, and a healing phase. *II. Response to extrinsic inflammatory stimuli* such as infection and chronic disease usually involves a host

of inflammatory mediators crossing the blood-brain barrier, triggering release of prostaglandins and central neuronal dysfunction and loss. *III. Response to intrinsic proteinopathy or neurodegenerative processes* such as aberrant beta-amyloid plaque or tau neurofibrillary tangles in Alzheimer disease is a slow, chronic inflammatory response that leads to synaptic dysfunction and neuronal loss.

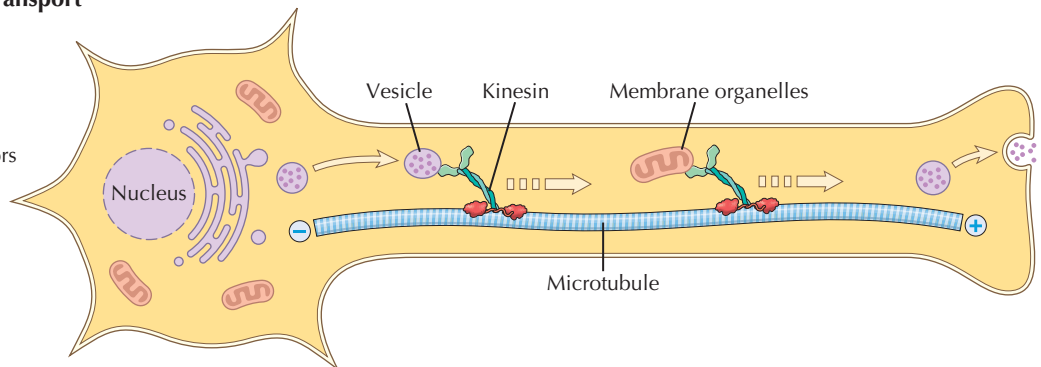


### I. Fast Anterograde Axonal Transport

100–400 mm/day in a saltatory fashion (start-stop-start)

Cargo includes:

- Synaptic vesicles and synaptic vesicle precursors
- Mitochondria and other membrane organelles
- Integral membrane proteins
- Secretory polypeptides
- Neurotransmitters
- Elements of smooth endoplasmic reticulum

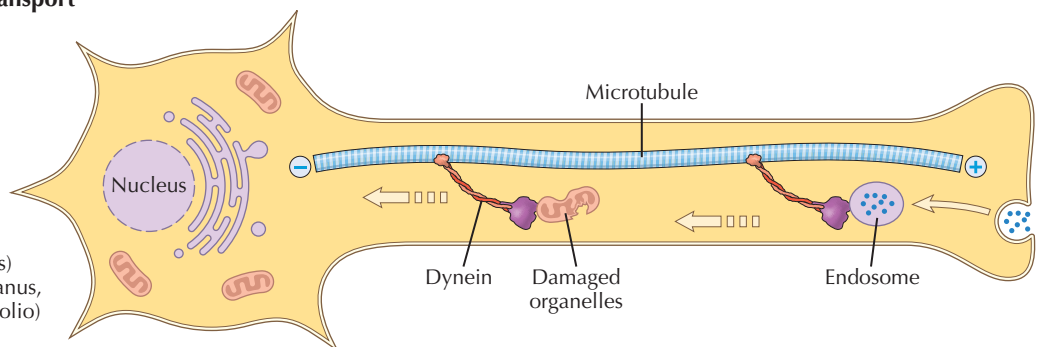


### II. Fast Retrograde Axonal Transport

200–270 mm/day

Cargo includes:

- Endosomes
- Damaged mitochondria and other organelles
- Elements of smooth endoplasmic reticulum
- Regulatory signals (growth factors and neurotrophins)
- Viruses and toxins (e.g., tetanus, herpes simplex, rabies, polio)



### III. Slow Axonal Transport (Anterograde Only)

Different substances move at two different speeds:

Slow Component a (SCa)

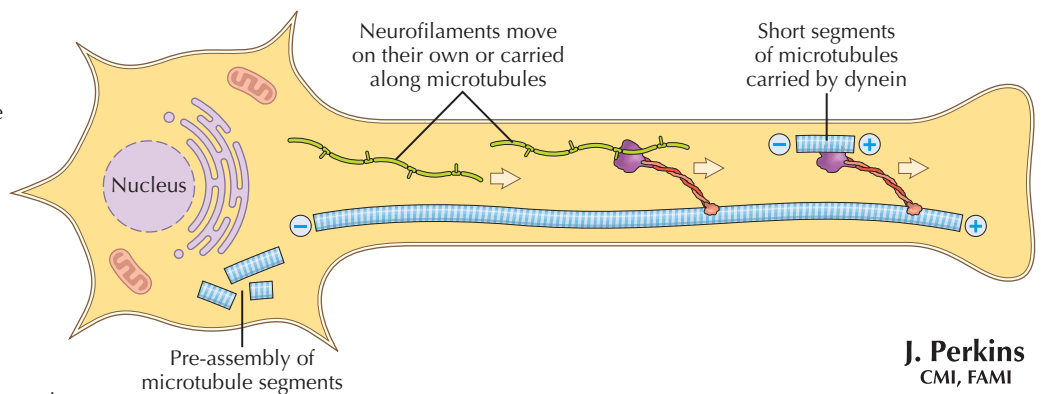
0.2–2.5 mm/day (rate of neurite elongation)

- Microtubules
- Neurofilaments
- Cytoskeletal proteins (e.g.,  $\alpha$  and  $\beta$  tubulin)

Slow Component b (SCb)

5.0–6.0 mm/day

- Cytosolic proteins
- Clathrin
- Calmodulin
- Soluble enzymes and other proteins

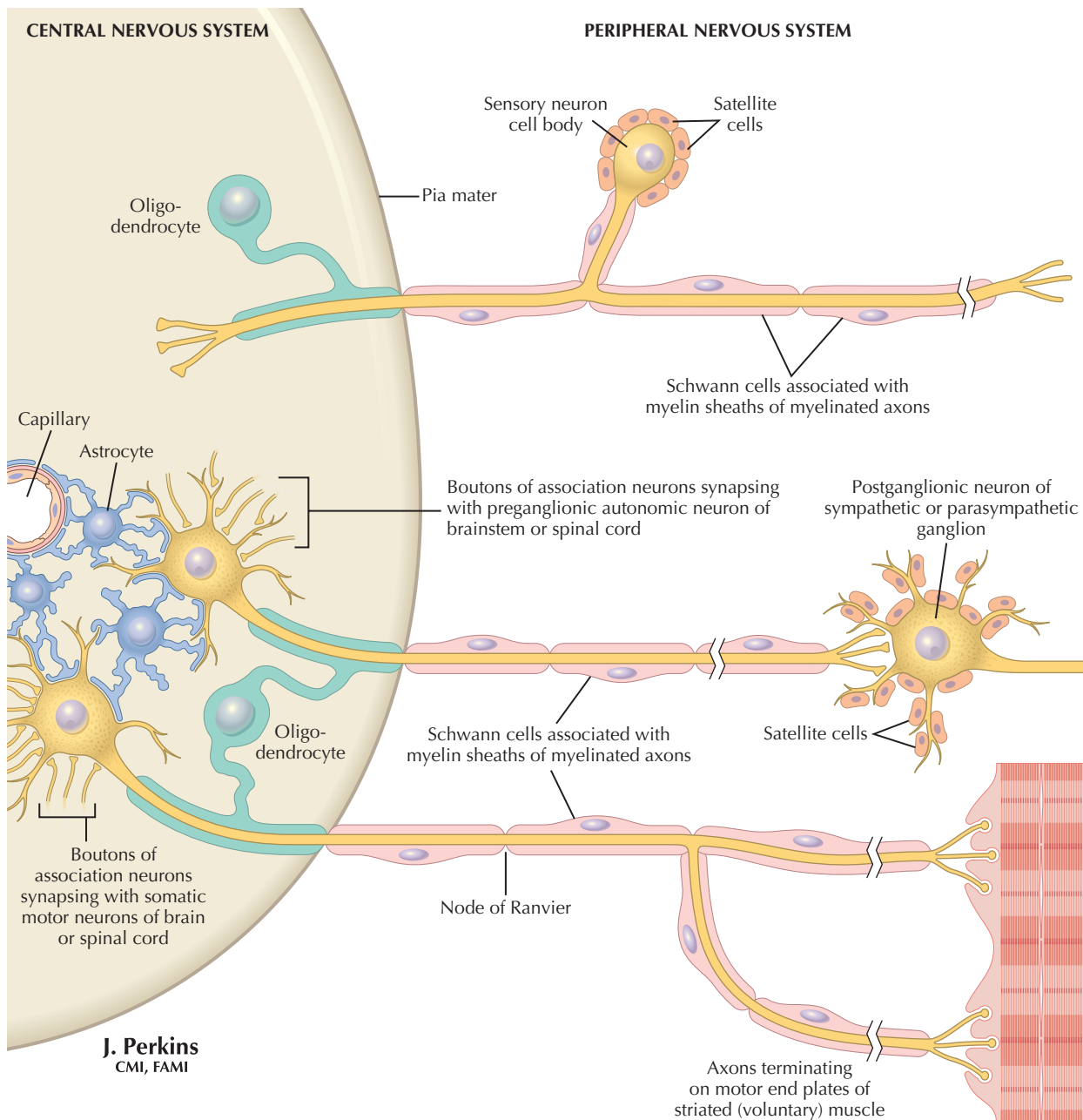


J. Perkins  
CMI, FAMI

## 1.14 AXONAL TRANSPORT IN THE CNS AND PNS

Intracellular organelles and molecules are transported both away from the cell body down the axon (anterograde transport) and toward the cell body from the axon (retrograde transport). *I. Fast anterograde transport* moves vesicles, organelles, membrane proteins, neurotransmitter elements, and smooth endoplasmic reticulum components at a rate of 100–400 mm/day in a stop-start fashion, using kinesin as a transport mechanism. *II. Fast retrograde transport* returns endosomes, damaged organelles, growth factors and trophic factors, and some viruses and toxins at a rate of 200–270 mm/

day, using dynein as a transport mechanism. Fast anterograde and retrograde transport mechanisms have been exploited in experimental neuroanatomical studies using labelled compounds (e.g., horseradish peroxidase, fluorogold) for retrograde tract tracing, and radiolabeled proteins for anterograde tract tracing. *III. Slow anterograde transport* carries microtubules, neurofilaments, and some cytoskeletal proteins at 0.2–2.5 mm/day (slow component a), and other enzymes and proteins at 5.0–6.0 mm/day (slow component b). This slow transport process is the rate-limiting factor governing axonal recovery after injury or insult; recovery usually proceeds (if it occurs at all) at approximately 1 mm/day.



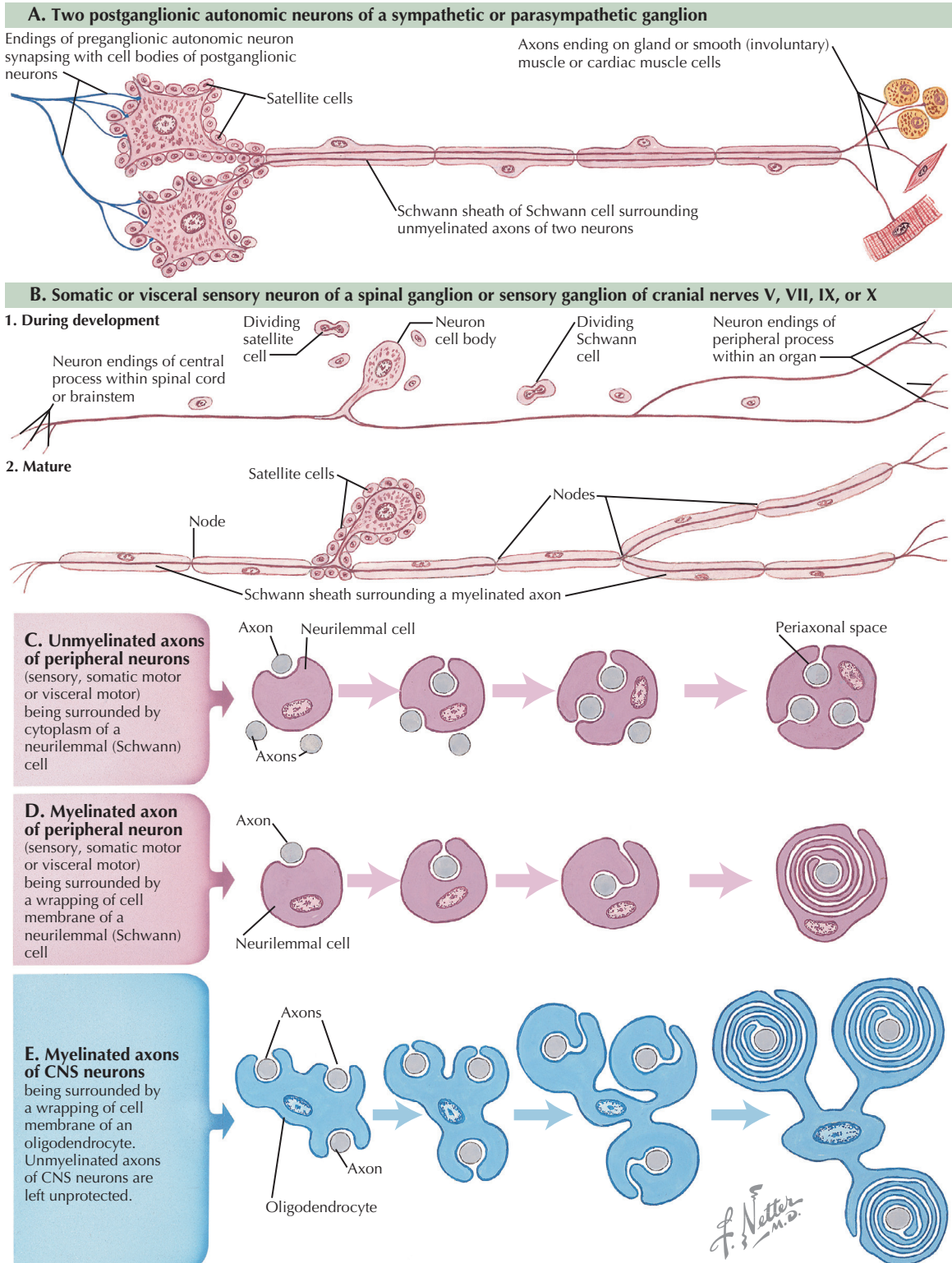
### 1.15 MYELINATION OF CNS AND PNS AXONS

Central myelination of axons is provided by oligodendroglia. Each oligodendroglial cell can myelinate a single segment of several separate central axons. In the PNS, sensory, motor, and preganglionic autonomic axons are myelinated by Schwann cells. A Schwann cell myelinates only a single segment of one axon. Unmyelinated sensory and autonomic postganglionic autonomic axons are ensheathed by a Schwann cell, which provides a single enwrapping arm of cytoplasm around each of several such axons. The space between adjacent myelin segments of an axon is called a node of Ranvier; this site of axon membrane contains sodium channels and allows the reinitiation of action potentials in the course of propagation down the axon, a process called saltatory conduction.

#### CLINICAL POINT

The integrity of the myelin sheath is essential for proper neuronal function in both the CNS and the PNS. Disruption of the myelin sheath around axons in either system results in the inability of the formerly myelinated axons to carry out their functional activities. In the CNS, the myelin sheath of central axons can be attacked in an autoimmune disease such as multiple sclerosis, resulting in a variety of symptoms, such as blindness, diplopia caused by disordered eye movements, loss of sensation, loss of coordination, paresis, and others. This condition may occur episodically, with intermittent remyelination occurring as the result of oligodendroglia proliferation and remyelination. In the PNS, a wide variety of insults, including exposure to toxins and the presence of diabetes or autoimmune Guillain-Barré syndrome, result in peripheral axonal demyelination, which is manifested mainly as sensory loss and paralysis or weakness. Remyelination also can occur around peripheral axons, initiated by the Schwann cells. Clinically, the status of axonal conduction is assessed by examining sensory evoked potentials in the CNS and by conduction velocity studies in the PNS.

## SHEATH AND SATELLITE CELL FORMATION

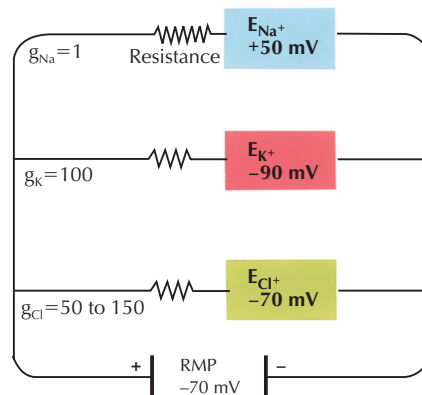
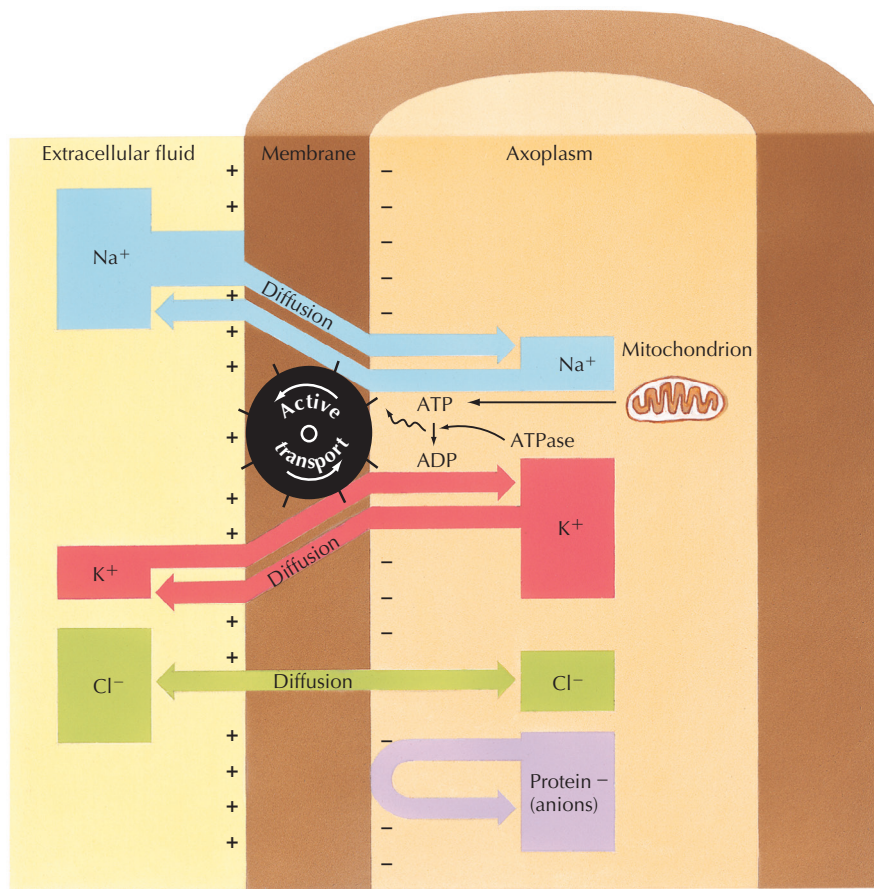


### 1.16 DEVELOPMENT OF MYELINATION AND AXON ENSHEATHMENT

Myelination requires a cooperative interaction between the neuron and its myelinating support cell. Unmyelinated peripheral axons are invested with a single layer of Schwann cell cytoplasm. When a peripheral axon at least 1 to 2  $\mu\text{m}$  in diameter triggers myelination, a Schwann cell wraps many layers of tightly packed cell membrane around a single segment of that axon. In the CNS, an oligodendroglia cell extends several arms

of cytoplasm, which then wrap multiple layers of tightly packed membrane around a single segment of each of several axons (or occasionally two autonomic preganglionic axons). Although myelination is a process that occurs most intensely during development, Schwann cells may remyelinate peripheral axons following injury, and oligodendroglial cells may proliferate and remyelinate injured or demyelinated central axons in diseases such as multiple sclerosis.





Equivalent circuit diagram;  
g is ion conductance across  
the membrane

*F. Netter M.D.*

## ELECTRICAL PROPERTIES

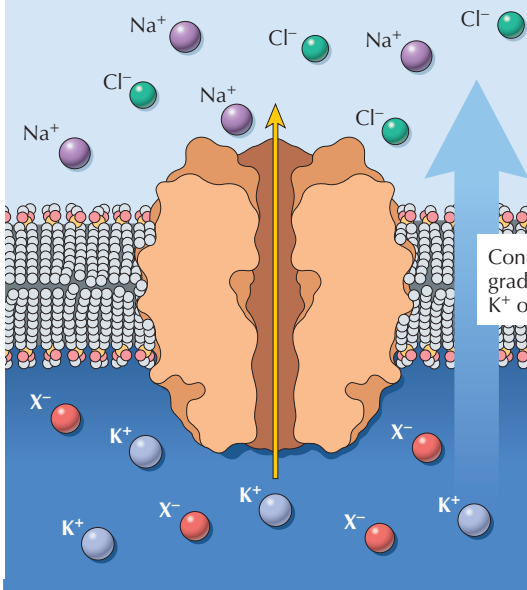
### 1.17 NEURONAL RESTING POTENTIAL

Cations (+) and anions (−) are distributed unevenly across the neuronal cell membrane because the membrane is differentially permeable to these ions. The uneven distribution depends on the forces of charge separation and diffusion. The permeability of the membrane to ions changes with depolarization (toward 0) or hyperpolarization (away from 0). The typical neuronal resting potential is approximately −90 mV with respect to the extracellular fluid. The extracellular concentrations of  $\text{Na}^+$  and  $\text{Cl}^-$  of 145 and 105 mEq/L, respec-

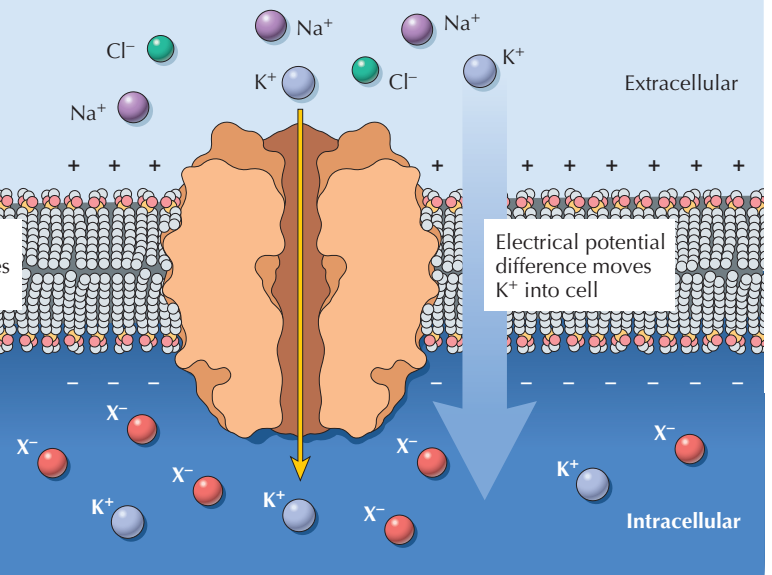
tively, are high compared to the intracellular concentrations of 15 and 8 mEq/L. The extracellular concentration of  $\text{K}^+$  of 3.5 mEq/L is low compared to the intracellular concentration of 130 mEq/L. The resting potential of neurons is close to the equilibrium potential for  $\text{K}^+$  (as if the membrane were permeable only to  $\text{K}^+$ ).  $\text{Na}^+$  is actively pumped out of the cell in exchange for inward pumping of  $\text{K}^+$  by the  $\text{Na}^+-\text{K}^+$ -ATPase membrane pump. Equivalent circuit diagrams for  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$ , calculated using the Nernst equation, are illustrated in the lower diagram.



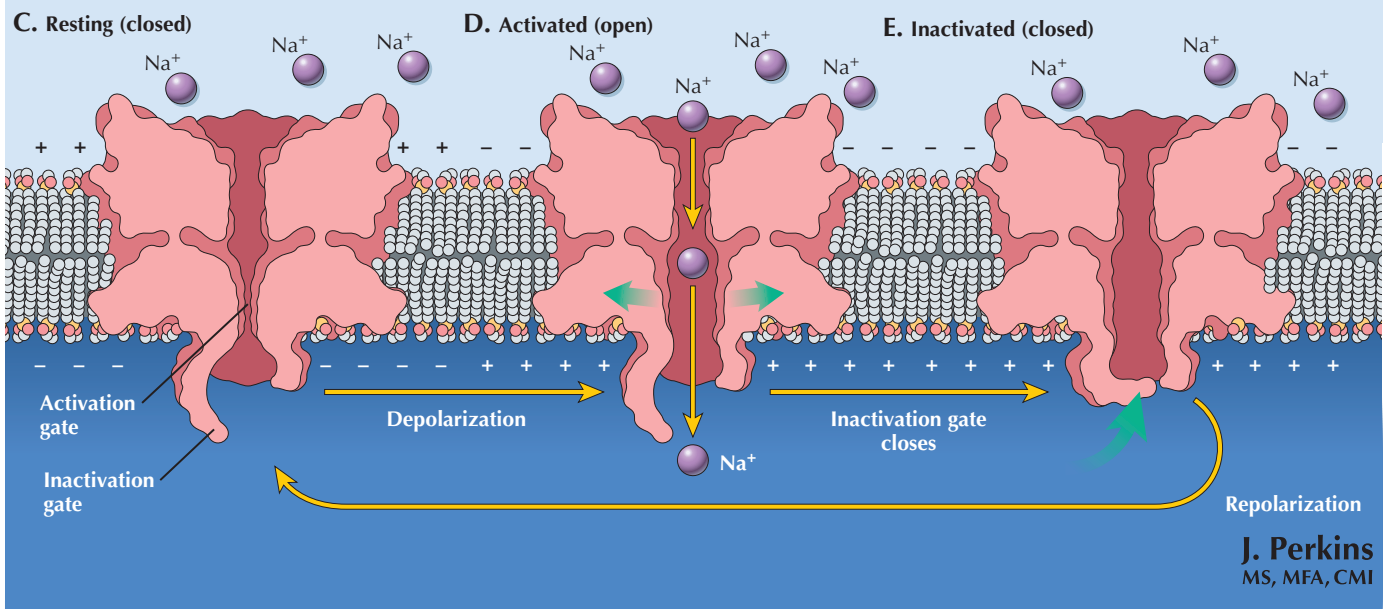
**A.** The movement of ions across the cell membrane is dependent upon both concentration and electrostatic forces. Ions flow from high concentrations to lower concentrations as depicted by the flow of  $K^+$  ions from inside the cell, where the concentration is high, to outside the cell, where the concentrations is lower.



**B.** Ions are attracted to charges of the opposite polarity. In this example,  $K^+$  ions flow from the extracellular environment, which is positive in relationship to the intracellular space, which is negative. Both concentration and electrostatic forces determine flow of ions. The equilibrium potential for the ion is the membrane potential at which a particular ion does not diffuse through the membrane in either direction.



**Three states of the sodium channel.** **C.** In the resting state, no ion flow occurs due to closure of the activation gate. **D.** When the membrane begins to depolarize, the activation channel opens and ion flow occurs. **E.** As the cell becomes depolarized, the inactivation gate closes and no further ion flow occurs. Only when the cell repolarizes does the sodium channel return to the resting state.

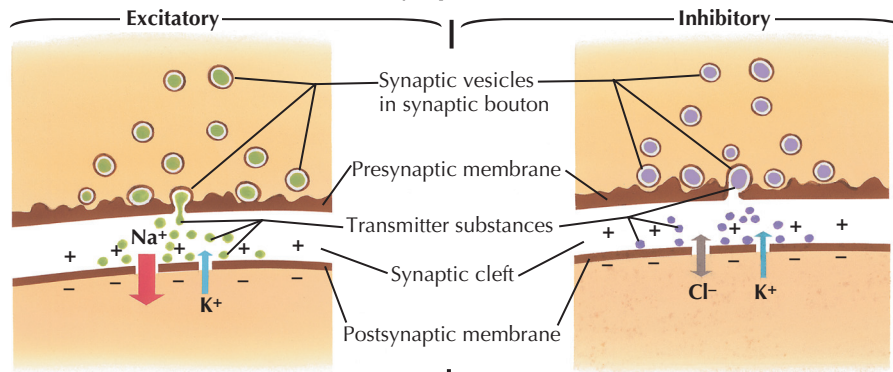


## 1.18 NEURONAL MEMBRANE POTENTIAL AND SODIUM CHANNELS

Illustrations of ion flow contributing to the neuronal resting potential and three states of the sodium channel in neuronal excitability.

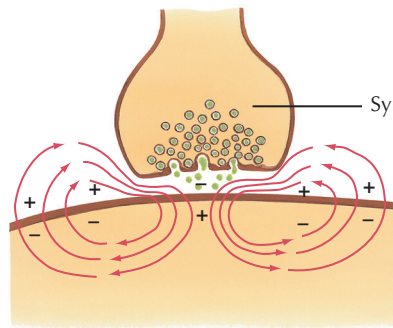
## Chemical Synaptic Transmission

## A. Ion movements

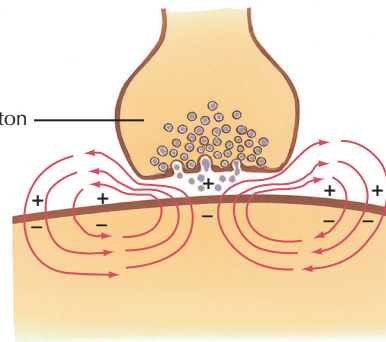


When impulse reaches excitatory synaptic bouton, it causes release of a transmitter substance into synaptic cleft. This increases permeability of postsynaptic membrane to  $\text{Na}^+$  and  $\text{K}^+$ . More  $\text{Na}^+$  moves into postsynaptic cell than  $\text{K}^+$  moves out, due to greater electrochemical gradient.

At inhibitory synapse, transmitter substance released by an impulse increases permeability of postsynaptic membrane to  $\text{K}^+$  and  $\text{Cl}^-$  but not  $\text{Na}^+$ .  $\text{K}^+$  moves out of postsynaptic cell.

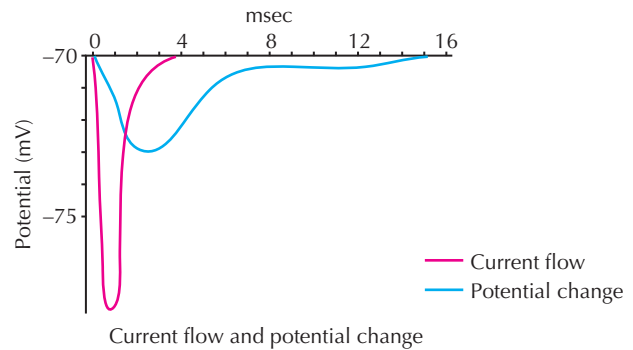
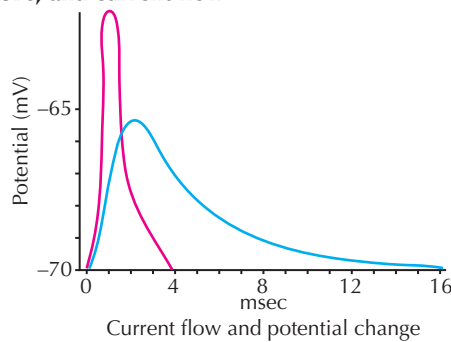


Resultant net ionic current flow is in a direction that tends to depolarize postsynaptic cell. If depolarization reaches firing threshold at the axon hillock, an impulse is generated in postsynaptic cell.



Resultant ionic current flow is in a direction that tends to hyperpolarize postsynaptic cell. This makes depolarization by excitatory synapses more difficult—more depolarization is required to reach threshold.

## B. EPSPs, IPSPs, and current flow

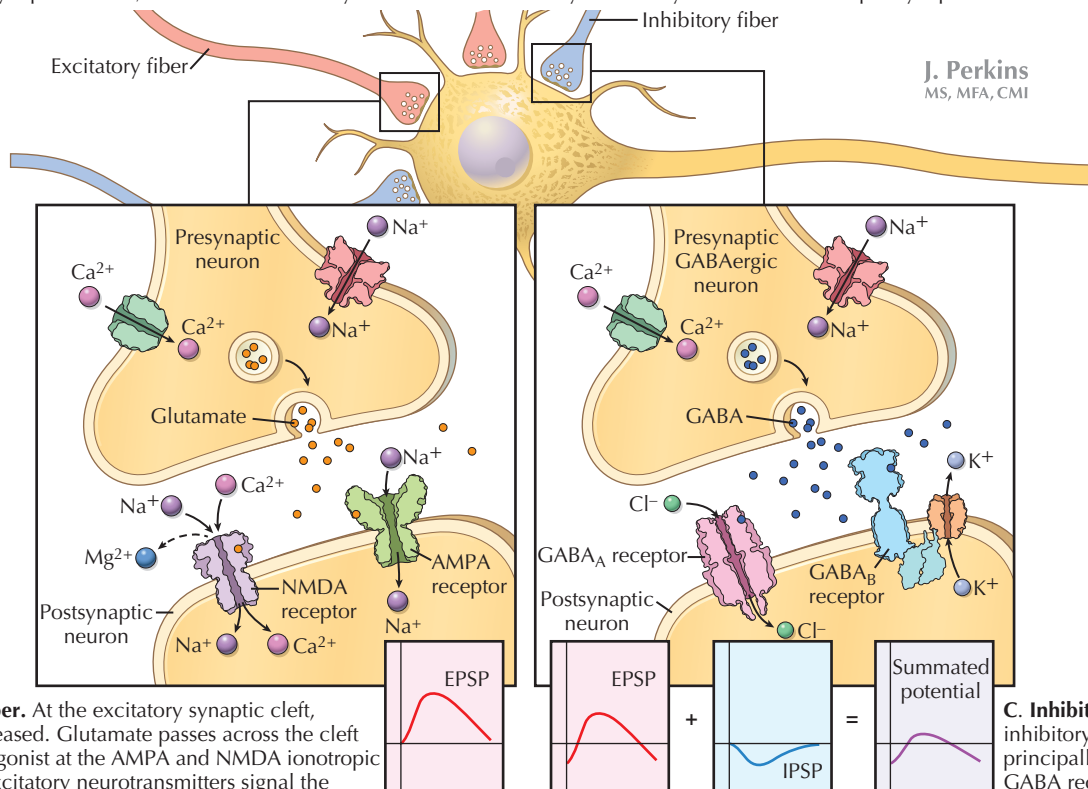


## 1.19 GRADED POTENTIALS IN NEURONS

**A, Ion movements.** Excitatory and inhibitory neurotransmissions are processes by which released neurotransmitter, acting on postsynaptic membrane receptors, elicits a local or regional perturbation in the membrane potential: (1) toward 0 (depolarization, excitatory postsynaptic potential; EPSP) via an inward flow of  $\text{Na}^+$  caused by increased permeability of the membrane to positively charged ions; or (2) away from 0 (hyperpolarization, inhibitory postsynaptic potential; IPSP) via an inward flow of  $\text{Cl}^-$  and a compensatory outward flow of  $\text{K}^+$  caused by increased membrane permeability to  $\text{Cl}^-$ . Following the action of neurotransmitters on the postsynaptic

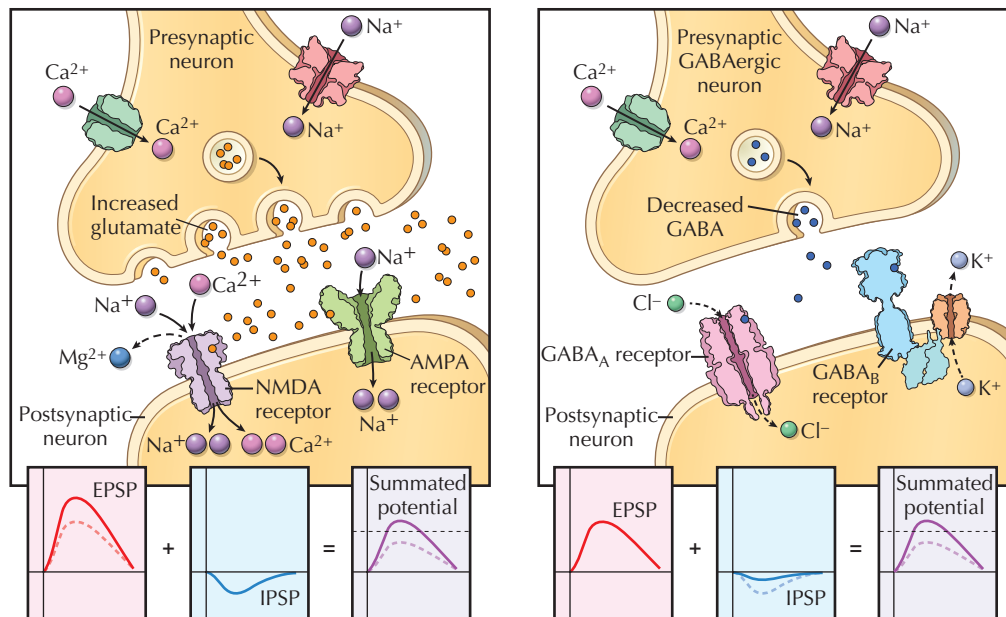
membrane, the resultant EPSPs and IPSPs exert local influences that dissipate over time and distance but contribute to the overall excitability and ion distribution in the neuron. It is unusual for a single excitatory input to generate sufficient EPSPs to bring about depolarization of the initial segment of the axon above threshold so that an action potential is fired. However, the influence of multiple EPSPs, integrated over space and time, may sum to collectively reach threshold. IPSPs reduce the ability of EPSPs to bring the postsynaptic membrane to threshold. **B, EPSPs, IPSPs, and current flow.** EPSP- and IPSP-induced changes in postsynaptic current (red) and potential (blue).

**A. Postsynaptic neuron at which several presynaptic afferent fibers terminate.** Fibers colored in pink convey excitatory information across the synaptic cleft to the postsynaptic neuron, whereas the inhibitory fiber is blue and conveys inhibitory information to the postsynaptic neuron.



**B. Excitatory fiber.** At the excitatory synaptic cleft, glutamate is released. Glutamate passes across the cleft and acts as an agonist at the AMPA and NMDA ionotropic receptor. The excitatory neurotransmitters signal the AMPA channel to open, permitting the inflow of  $\text{Na}^+$ . This results in depolarization in the membrane potential so that the difference in potential across the membrane is shifted toward the positive, i.e., depolarization. With depolarization, there is a release of  $\text{Mg}^{2+}$  from the NMDA receptor, permitting  $\text{Na}^+$  and  $\text{Ca}^{2+}$  ions to enter the postsynaptic neuron. An excitatory postsynaptic potential (EPSP) is generated.

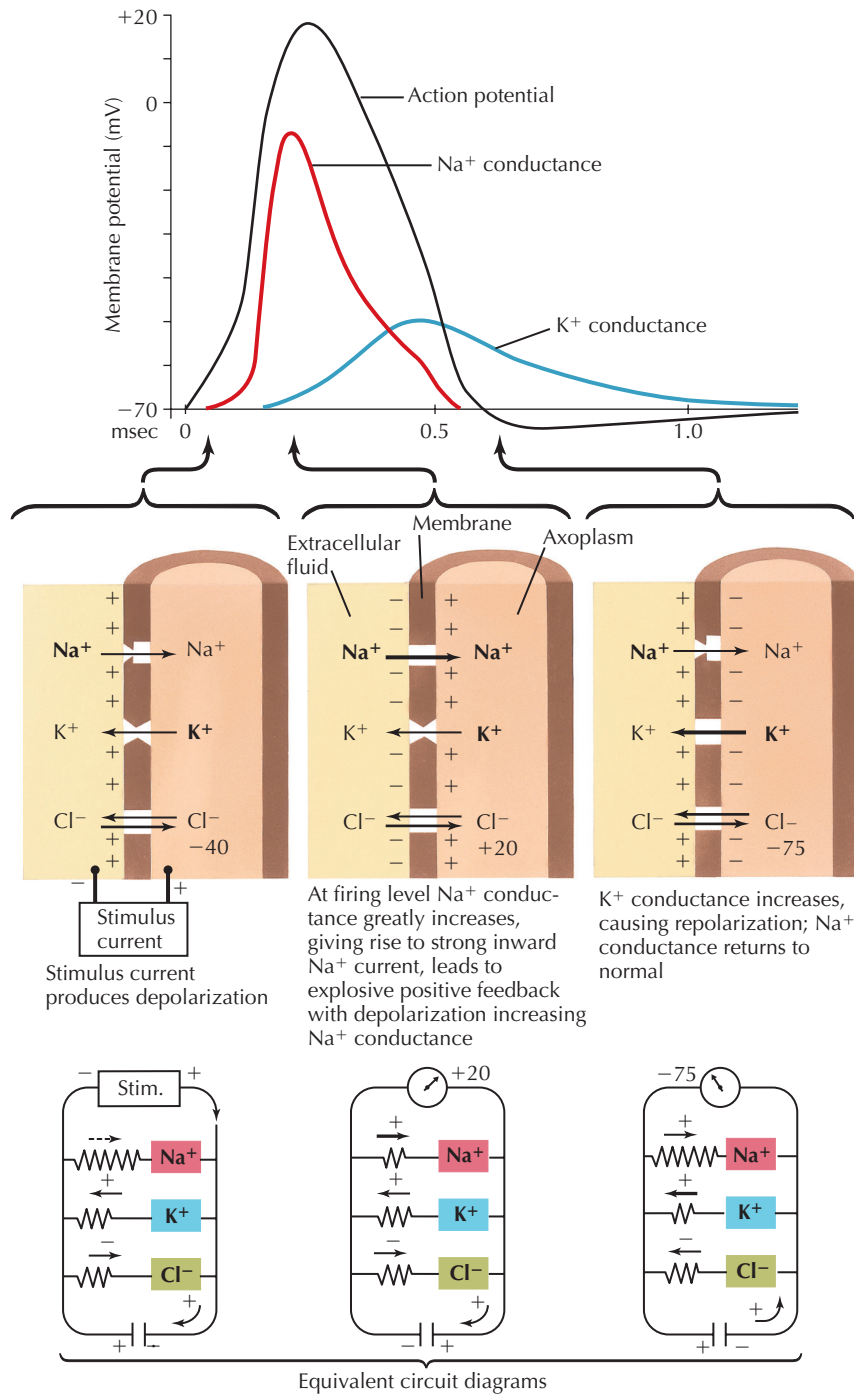
**C. Inhibitory fiber.** The inhibitory neurotransmitters, principally GABA, act on GABA receptors in the postsynaptic neuron membrane, permitting the entry of  $\text{Cl}^-$  ions, shifting the membrane potential to a more negative potential, i.e., hyperpolarization. An inhibitory postsynaptic potential (IPSP) is generated. In normal synaptic transmission, there is a balance between excitatory and inhibitory neurotransmitters so that the summation of EPSP and IPSP maintains the polarization of the membrane at a level below the threshold at which bursts of firing occur, termed the resting potential.



**D. Increase in glutamate EPSP.** With an increase in excitatory neurotransmitters, the postsynaptic neuron membrane becomes more positive, producing an increase in EPSP. The summation of the excitatory and inhibitory signals moves across the threshold value, and an action potential occurs.

**E. Decrease in IPSP.** When there is a decrease in inhibitory neurotransmitters, the IPSP decrease and the postsynaptic neuron membrane becomes more positive. The summation of the excitatory and inhibitory signals moves across the threshold value and an action potential is fired.

## 1.20 MECHANISMS OF EXCITATORY POSTSYNAPTIC POTENTIALS AND INHIBITORY POSTSYNAPTIC POTENTIALS

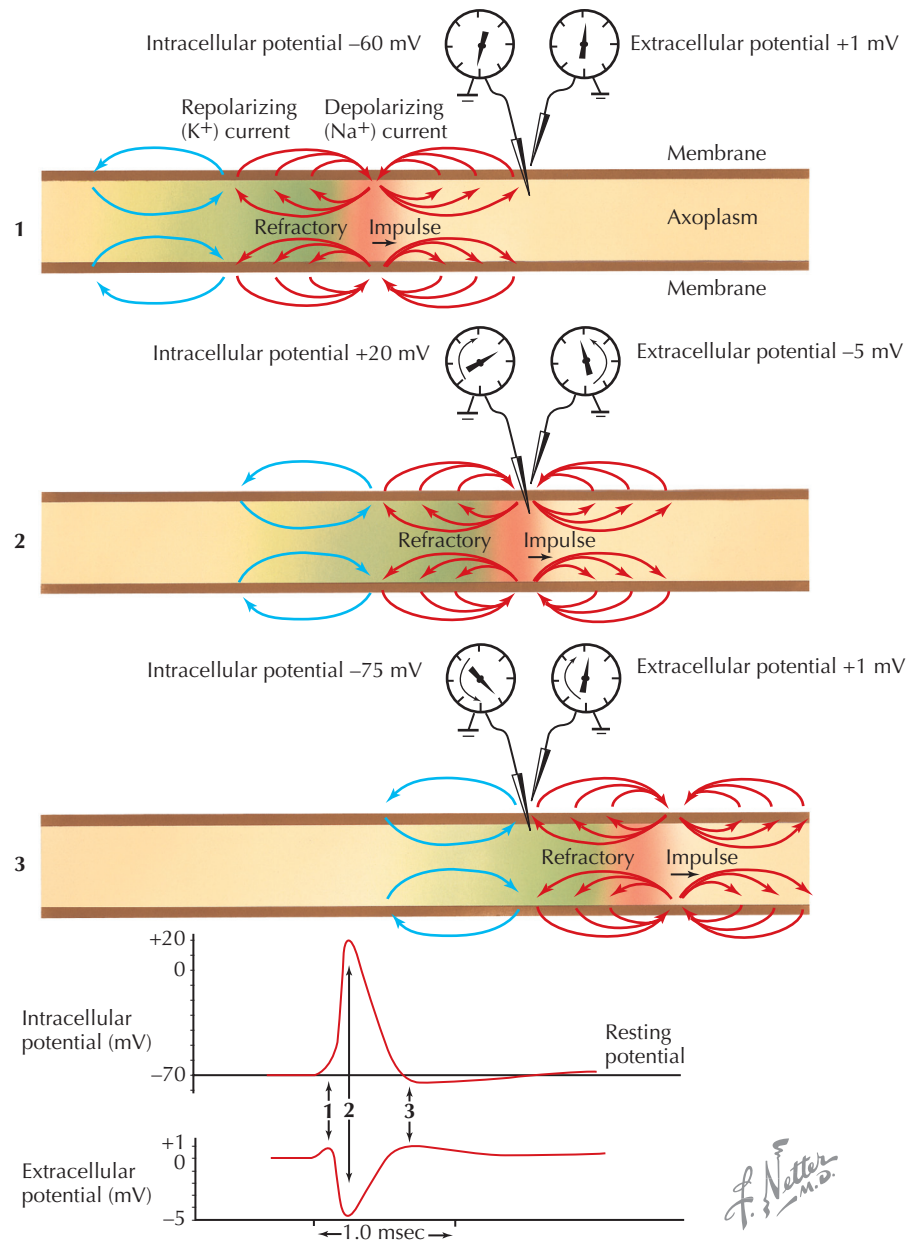


## 1.21 ACTION POTENTIALS

Action potentials (APs) are all-or-nothing, nondecremental, electrical potentials that allow an electrical signal to travel for very long distances (a meter or more) and trigger neurotransmitter release through electrochemical coupling (excitation-secretion coupling). APs are usually initiated at the initial segment of axons when temporal and spatial summation of EPSPs cause sufficient excitation (depolarization) to open  $\text{Na}^+$  channels, allowing the membrane to reach threshold. Threshold is the point at which  $\text{Na}^+$  influx through these  $\text{Na}^+$  channels

cannot be countered by efflux of  $\text{K}^+$ . When threshold is reached, an action potential is fired. As the axon rapidly depolarizes during the rising phase of the AP, the membrane increases its  $\text{K}^+$  conductance, which then allows efflux of  $\text{K}^+$  to counter the rapid depolarization and bring the membrane potential back toward its resting level. Once the action potential has been initiated, it rapidly propagates down the axon by reinitiating itself at each node of Ranvier (myelinated axon) or adjacent patch of membrane (unmyelinated axon) by locally bringing that next zone of axon membrane to threshold.





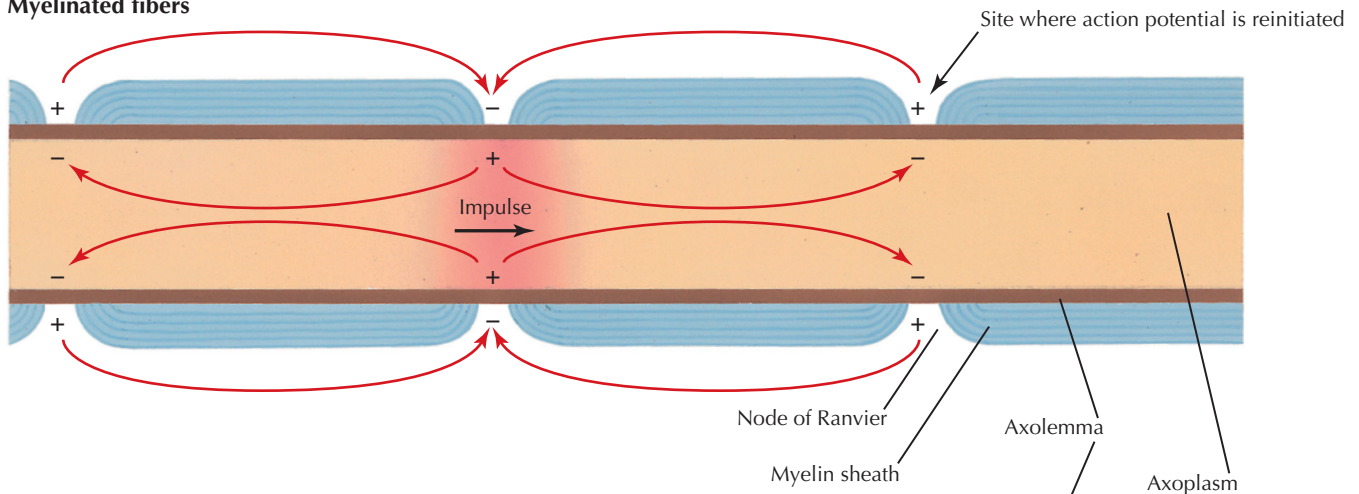
## 1.22 PROPAGATION OF THE ACTION POTENTIAL

When an AP is initiated at a specific site of the axonal membrane (usually the initial segment), the inward flow of  $\text{Na}^+$  alters the extracellular ion environment, causing a local flow of charge from adjacent regions of the axon. This induces a depolarized state in the adjacent node of Ranvier (myelinated axon) or patch of axonal membrane (unmyelinated axon), bringing that region to threshold and resulting in the reinitiation of the action potential. The presence of myelination along axonal segments results in the reinitiation of the action potential at the next node, thus hastening the velocity of conduction of the AP. The resultant appearance of the AP skipping from node to node down the axon is called *saltatory conduction*.

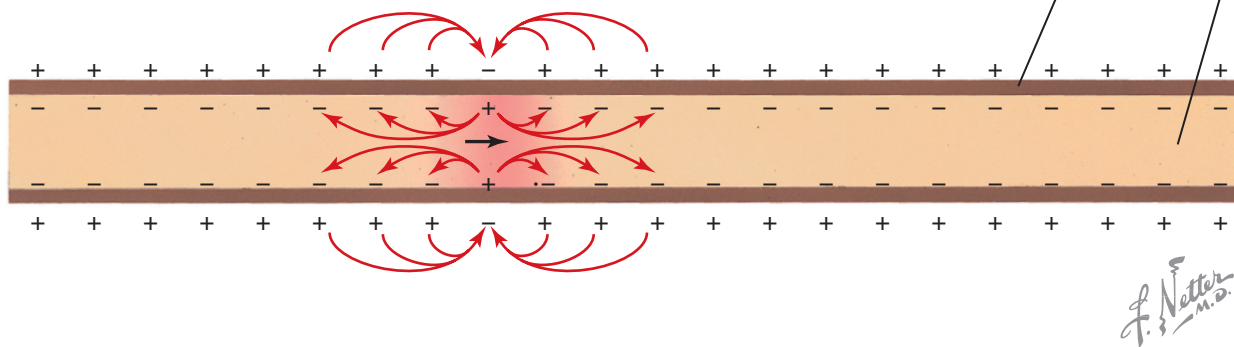
### CLINICAL POINT

An action potential is an explosive reversal of the neuronal membrane potential that takes place because of an increase in  $\text{Na}^+$  conductance induced by depolarization, usually due to the cumulative effects of graded potentials from incoming neurotransmitters; this explosive reversal is followed later by an increase in  $\text{K}^+$  conductance, restoring the membrane back toward the resting potential. This process normally takes place at the initial segment of an axon. The conduction of an AP down a myelinated axon, saltatory conduction, requires the reinitiation of the AP at each bare patch of axonal membrane, a node of Ranvier. The reinitiation of the AP occurs because of a voltage change at the next node brought about by passive current flow from the AP at its present site. If several nodes distal to the site of AP propagation are blocked with a local anesthetic, preventing  $\text{Na}^+$  conductance, then the AP will die, or cease, because the closest fully functional, nonblocked node is too far from the point of AP propagation to reach threshold by means of passive current flow. This mechanism of blocking reinitiation of the action potential at nodes of Ranvier underlies the use of the *-caine* derivatives, as in novocaine and xylocaine, for local anesthesia during surgical and dental procedures.

### A. Myelinated fibers



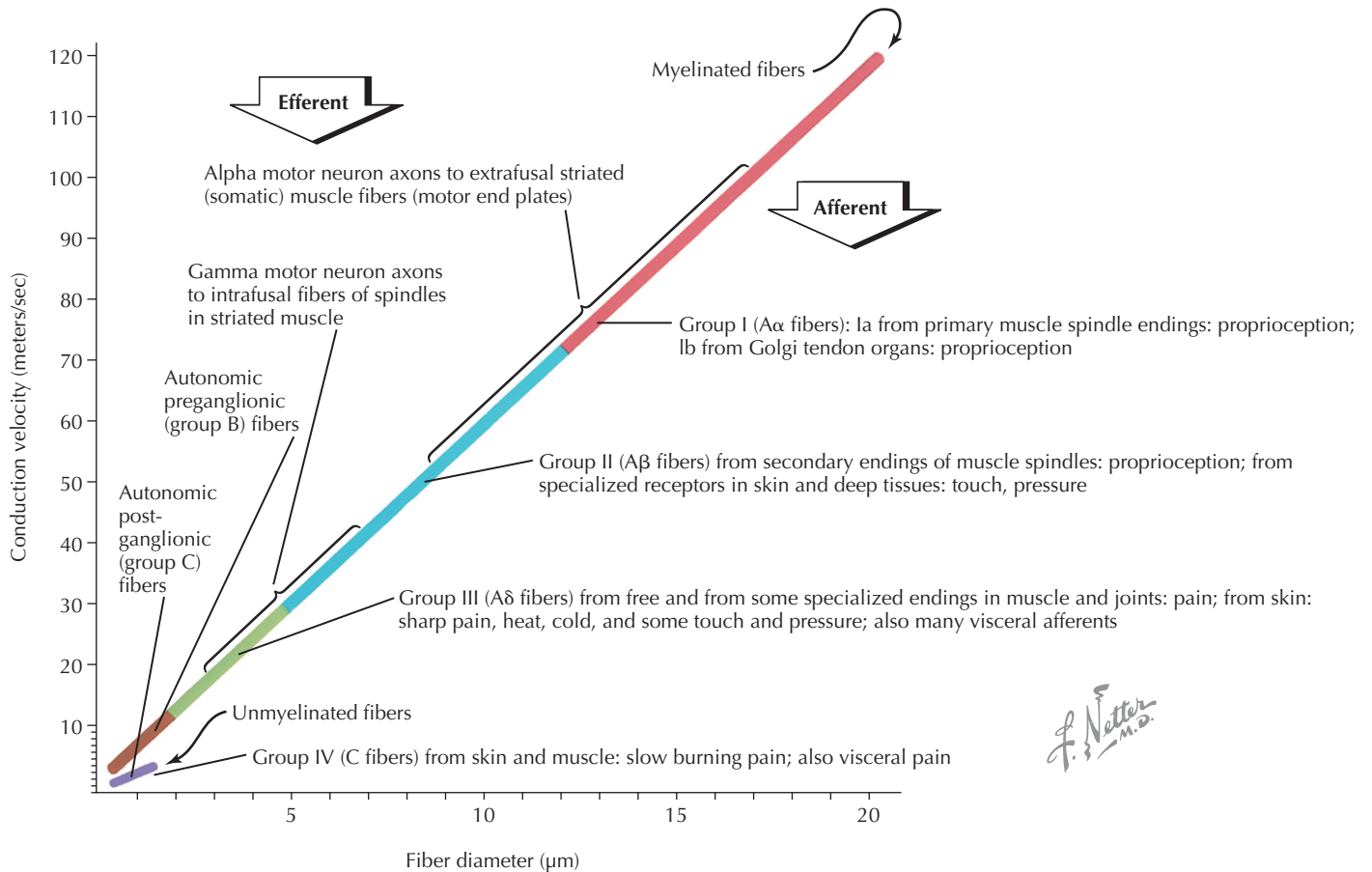
### B. Unmyelinated fibers



## 1.23 CONDUCTION VELOCITY

**A,** The speed of propagation increases with larger axonal diameter and in the presence of a myelin sheath. In myelinated axons the AP is propagated from node to node by saltatory

conduction. **B,** The AP travels down the unmyelinated axon by depolarizing adjacent patches of membrane, leading to reinitiation of the action potential.



### 1.24 CLASSIFICATION OF PERIPHERAL NERVE FIBERS BY SIZE AND CONDUCTION VELOCITY

Unmyelinated peripheral nerve fibers (1 to 2  $\mu\text{m}$  in diameter) conduct APs slowly (1 to 2 m/sec) because propagation requires reinitiation of the AP at each adjacent patch of axonal membrane along the entire course of the axon. These peripheral fibers are called group IV fibers. Myelinated peripheral nerve fibers (2 to 20+  $\mu\text{m}$  in diameter) conduct APs rapidly (2 to 120+ m/sec) because propagation is aided by the distant spacing of nodes of Ranvier resulting from the successive internodal myelin sheaths. The larger diameter axons conduct APs the most rapidly. Clinical conduction-velocity studies can document the conduction velocity of successive classes of myelinated peripheral nerve fibers (group I, II, and III fibers), and they provide evidence of normal or altered nerve conduction and possibly function. Conduction velocity is measured by placing a stimulating electrode at a specific site (in the popliteal fossa) where a current can initiate APs in axons in a specific nerve. Recording electrodes are placed at a distant site,

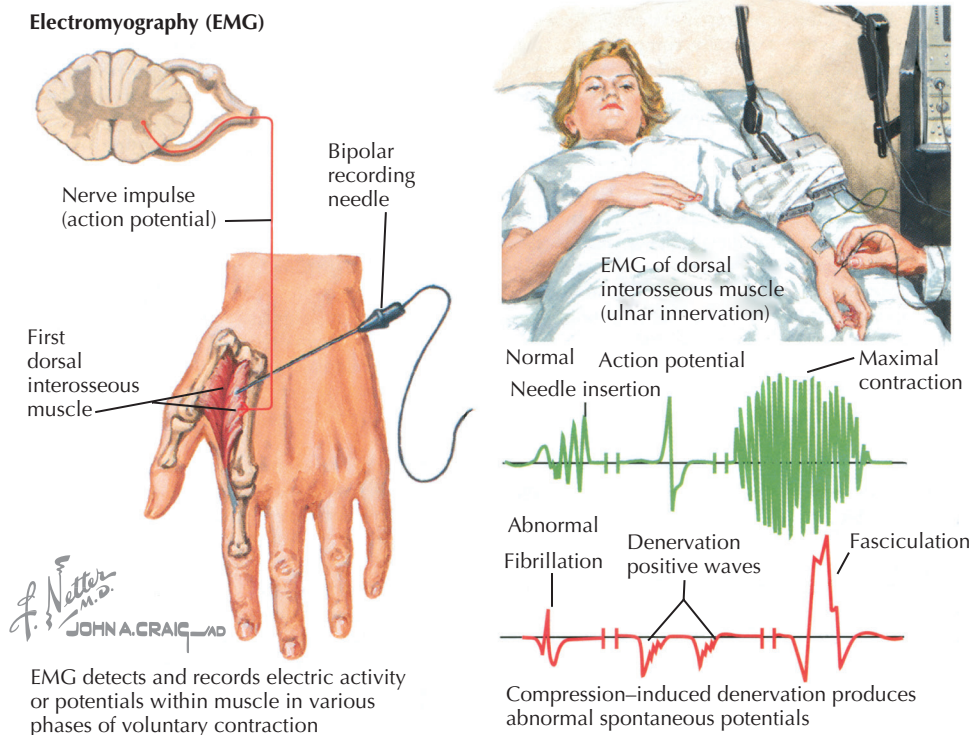
where muscle contractions can be measured and where the time delay of conduction of APs in axons can be measured. The classification system of myelinated nerve fibers in the figure is accompanied by descriptions of the functional types of axons included in each group.

#### CLINICAL POINT

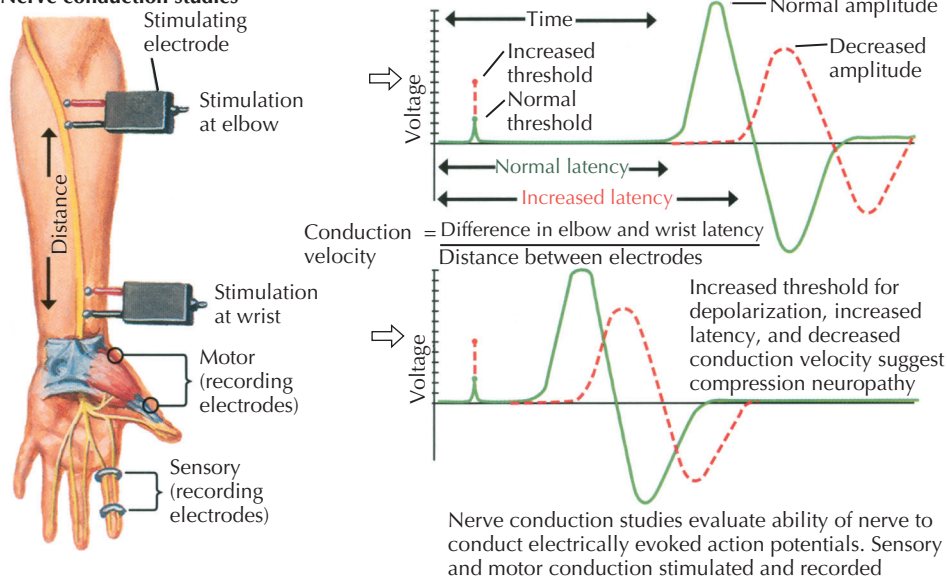
Peripheral axons larger than approximately 2  $\mu\text{m}$  in diameter trigger the process of myelination by adjacent Schwann cells. Peripheral axons of different sizes subserve different functions and are subject to damage by a variety of separate insults. Thus, small-fiber neuropathies, such as leprosy, damage pain, and temperature sensation (via small-diameter axons) and can affect these modalities without concomitant damage to discriminative touch, LMN function, or Ia afferent reflex activity. In contrast, damage to large-diameter axons, as seen in demyelinating neuropathies, can result in flaccid paralysis with loss of tone and reflexes (motor axons) and loss of fine, discriminative sensation (sensory axons) without loss of autonomic functions or loss of pain and temperature sensation, which are carried in part by small unmyelinated axons.

### Electrodiagnostic Studies in Compression Neuropathy

#### Electromyography (EMG)



#### Nerve conduction studies

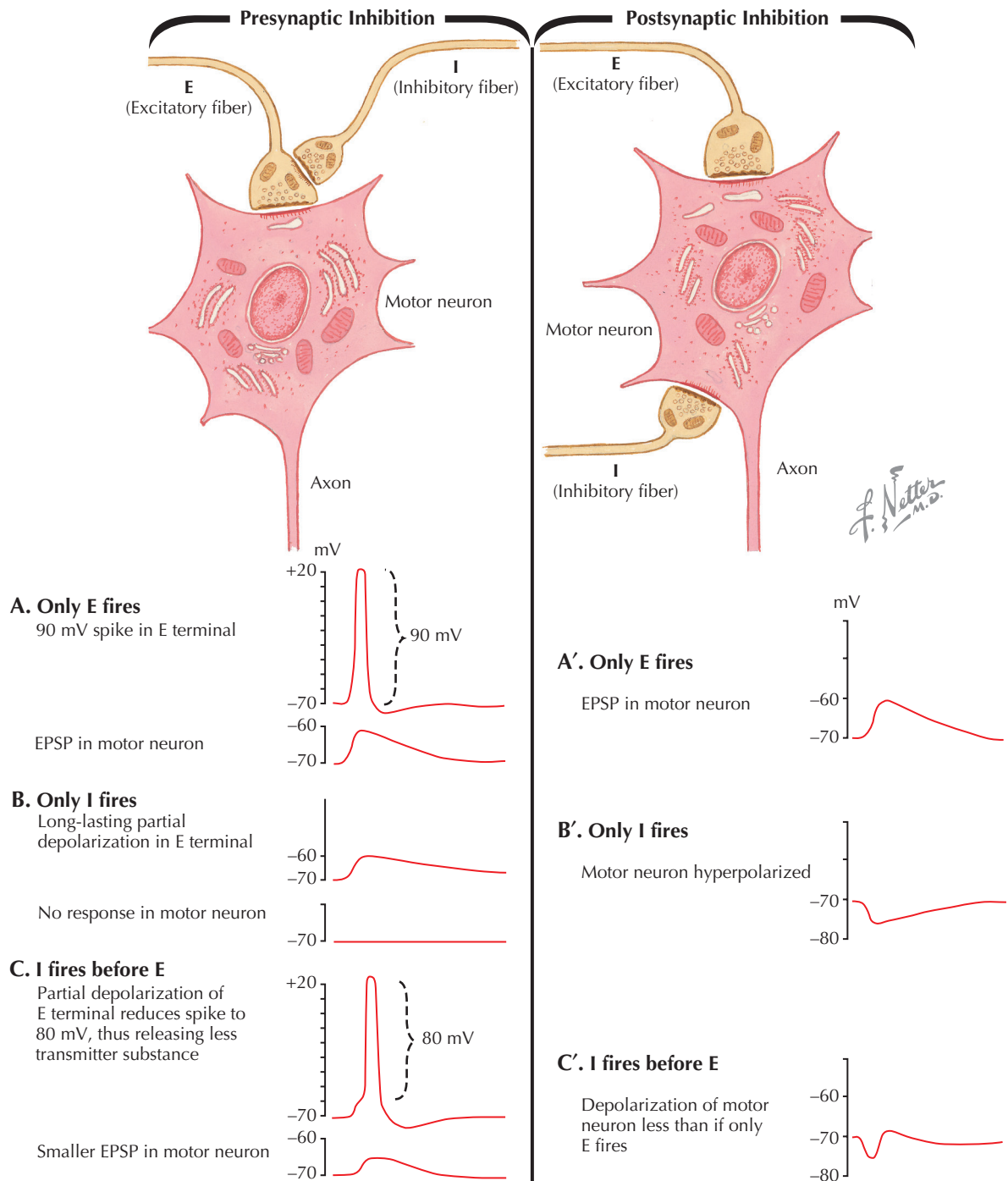


## 1.25 ELECTROMYOGRAPHY AND CONDUCTION VELOCITY STUDIES

Electromyography detects and records electrical activity within muscles in various phases of voluntary contraction. These studies are useful for diagnosing myopathies and axonal

damage in neuropathies. Nerve conduction velocity studies assess the ability of nerves (especially myelinated nerve fibers) to conduct electrically evoked APs in sensory and motor axons. Conduction velocity studies are particularly helpful in evaluating damage to myelinated axons.

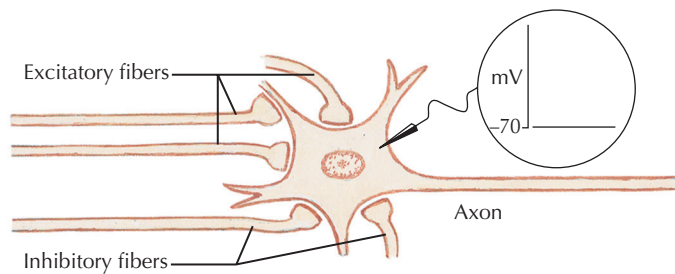




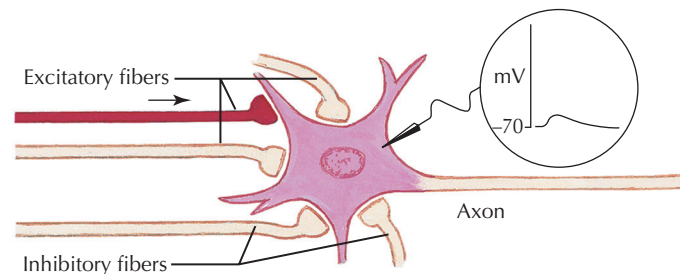
### 1.26 PRESYNAPTIC AND POSTSYNAPTIC INHIBITION

Inhibitory synapses modulate neuronal excitability. Presynaptic inhibition (left) and postsynaptic inhibition (right) are shown in relation to a motor neuron. Postsynaptic inhibition

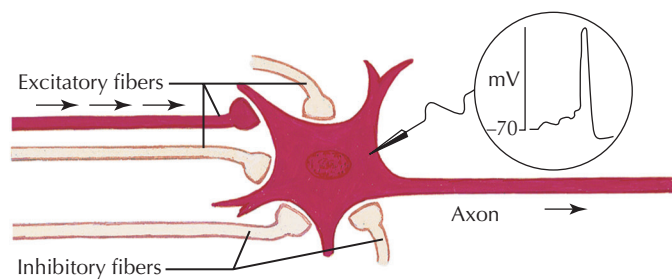
causes local hyperpolarization at the postsynaptic site. Presynaptic inhibition involves the depolarization of an excitatory axon terminal, which decreases the amount of  $\text{Ca}^{2+}$  influx that occurs with depolarization of that excitatory terminal, thus reducing the resultant EPSP at the postsynaptic site.



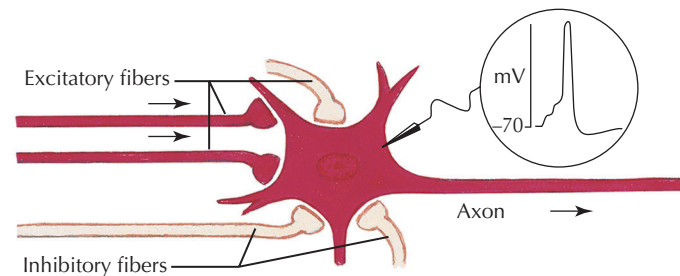
**A. Resting state:** motor nerve cell shown with synaptic boutons of excitatory and inhibitory nerve fibers ending close to it



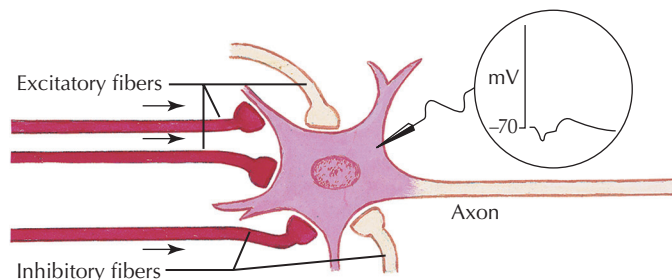
**B. Partial depolarization:** impulse from one excitatory fiber has caused partial (below firing threshold) depolarization of motor neuron



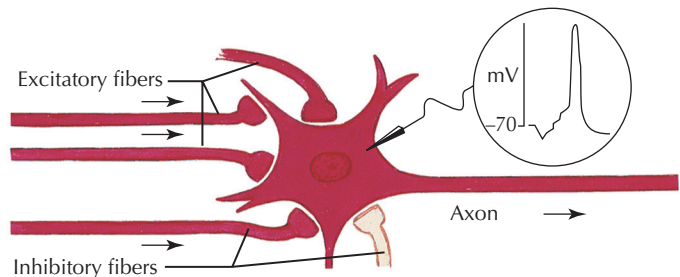
**C. Temporal excitatory summation:** a series of impulses in one excitatory fiber together produce a suprathreshold depolarization that triggers an action potential



**D. Spatial excitatory summation:** impulses in two excitatory fibers cause two synaptic depolarizations that together reach firing threshold, triggering an action potential



**E. Spatial excitatory summation with inhibition:** impulses from two excitatory fibers reach motor neuron but impulses from inhibitory fiber prevent depolarization from reaching threshold



**E. (continued):** motor neuron now receives additional excitatory impulses and reaches firing threshold despite a simultaneous inhibitory impulse; additional inhibitory impulses might still prevent firing

■ Axon(s) activated in each scenario

*F. Netter M.D.*

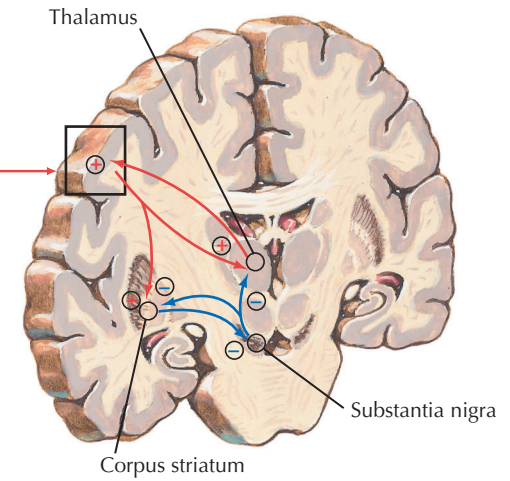
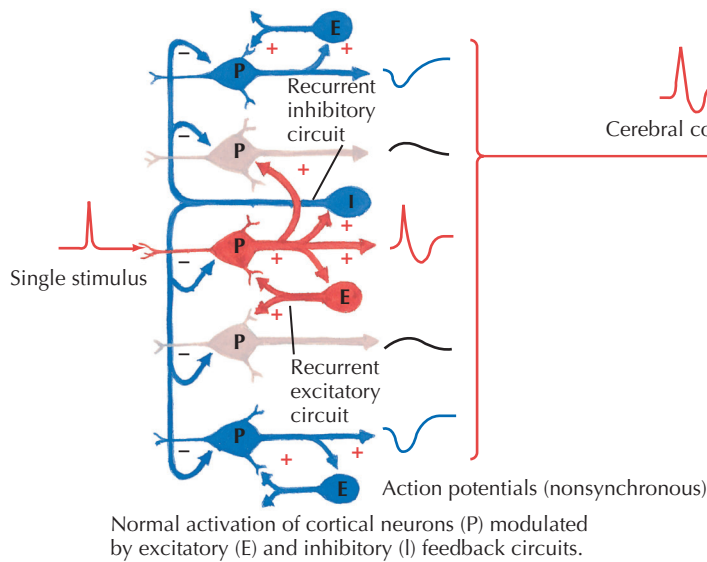
## 1.27 SPATIAL AND TEMPORAL SUMMATION

Neurons receive multiple excitatory and inhibitory inputs. **C**, Temporal summation occurs when a series of subthreshold EPSPs in one excitatory fiber produce an AP in the postsynaptic cell. This occurs because the EPSPs are superimposed on each other temporally before the local region of membrane has completely returned to its resting state. **D**, Spatial summa-

tion occurs when subthreshold impulses from two or more synapses trigger an AP because of synergistic interactions. **E**, Both temporal and spatial summation can be modulated by simultaneous inhibitory input. Inhibitory and excitatory neurons use a wide variety of neurotransmitters, whose actions depend on the ion channels opened by the ligand-receptor interactions.

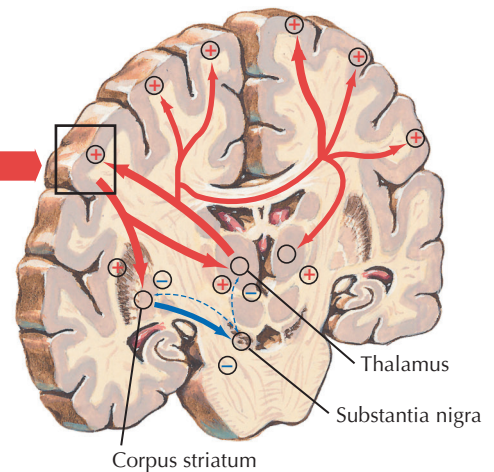
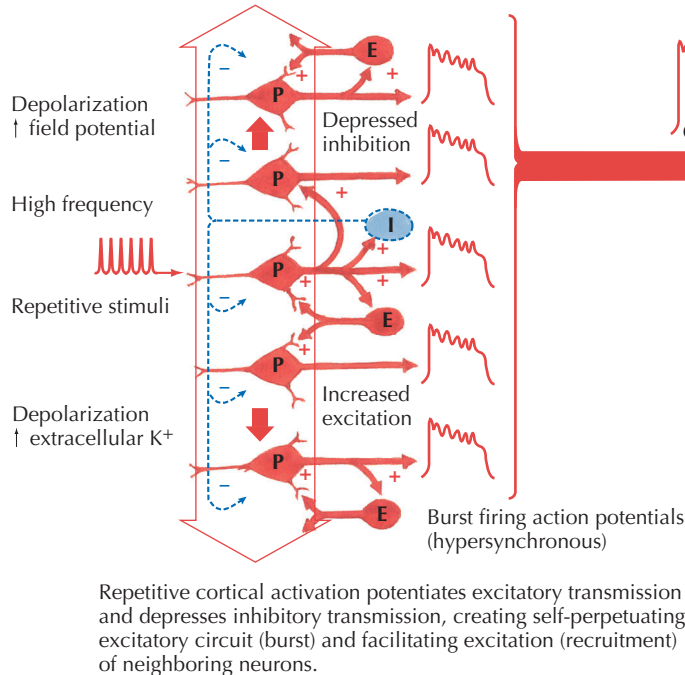
## Origin and Spread of Seizures

### A. Normal firing pattern of cortical neurons



Excitatory pathways between cerebral cortex and thalamus modulated by tonic midbrain inhibitory stimuli.

### B. Epileptic firing pattern of cortical neurons



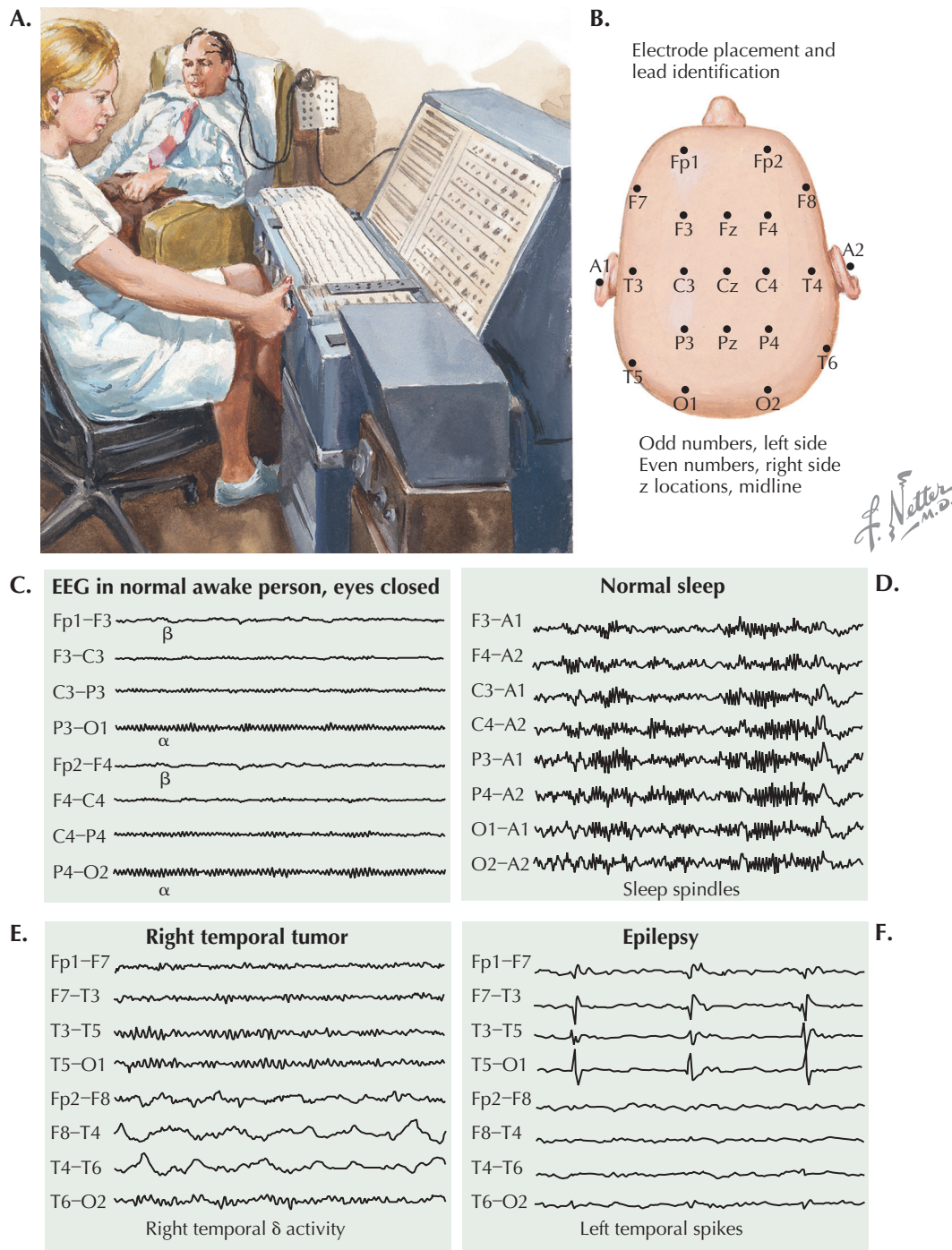
Cortical bursts to corpus striatum and thalamus block inhibitory projections and create self-perpetuating feedback circuit.

JOHN A. CRAIG, MD

## 1.28 NORMAL ELECTRICAL FIRING PATTERNS OF CORTICAL NEURONS AND THE ORIGIN AND SPREAD OF SEIZURES

The collective electrical activity of the cerebral cortex can be monitored by electroencephalography (EEG). Normal cortical electrical activity reflects the summation of excitatory and inhibitory actions, which is modulated through feedback

circuits. Thalamic inputs to the cortex can drive electrical excitability; the midbrain can provide inhibitory control over this process. Repetitive cortical activation can dampen inhibition, enhance excitatory feedback circuits, and recruit repetitive excitatory circuitry in adjacent cortical neurons. These self-perpetuating excitatory feedback circuits can initiate and spread seizure activity.

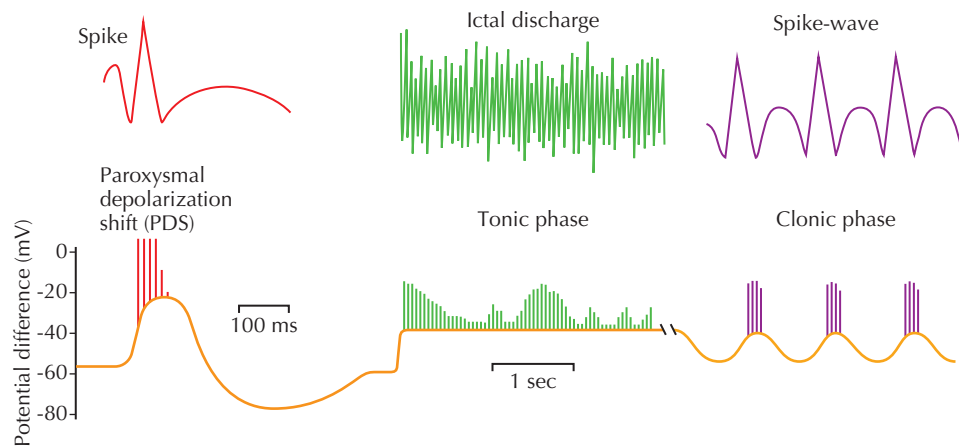


### 1.29 ELECTROENCEPHALOGRAPHY

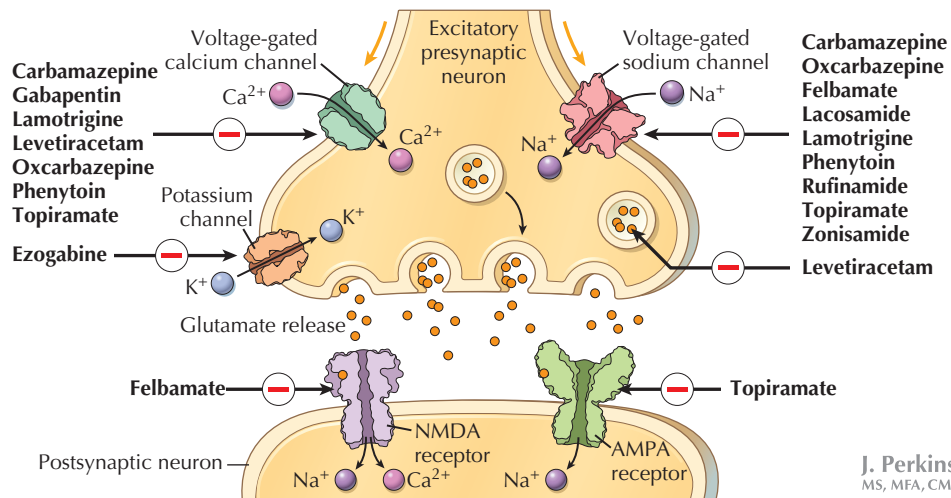
EEG permits the recording of the collective electrical activity of the cerebral cortex as a summation of activity measured as a difference between two recording electrodes. Recording electrodes (leads) are placed on the scalp on at least 16 standard sites, and recordings of potential differences between key electrodes are obtained. The principal wave forms recorded in the EEG are alpha (9 to 10 Hz, occipital location, predominant activity in adults, awake in resting state with eyes closed); beta (20 to 25 Hz, frontal and precentral locations, prominent in wakefulness, seen in light sleep); delta (2 to 2.5 Hz, frontal and central location, not prominent in wakefulness, generalized in

deep sleep and coma or toxic states); and theta (5 to 6 Hz, central location, constant and not prominent when awake and active, sometimes generalized when drowsy). Electrode placement is shown in figure B. Examples are provided of a normal EEG taken when the patient is awake with eyes closed (C), and when sleeping normally (D). Abnormal patterns of activity can be seen in the presence of tumors (E) and in seizures (F); for example, the spike-and-wave appearance in a generalized tonic-clonic seizure (generalized fast repetitive spikes and generalized spikes and slow waves, respectively); and a 3 Hz spike-and-wave EEG in the case of an absence seizure.



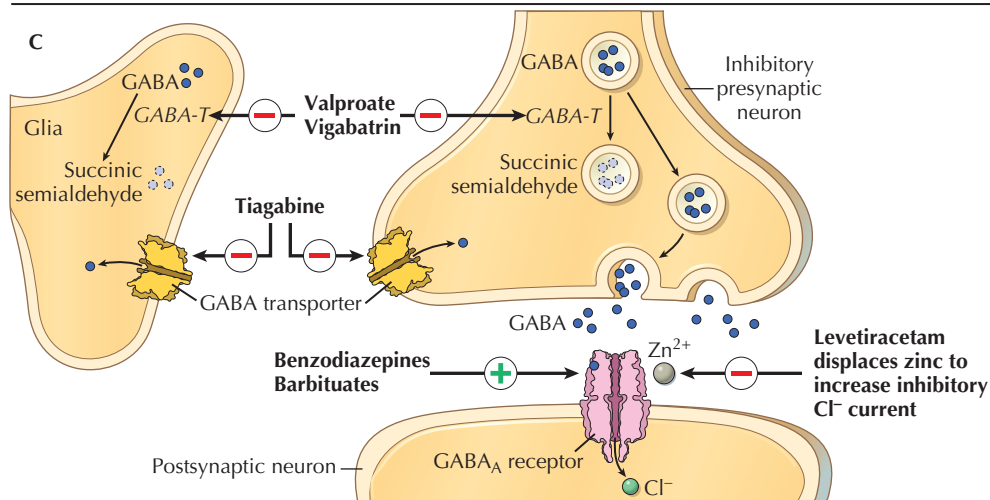


**A.** Paroxysmal depolarization shift (PDS) is a cellular marker of epilepsy and consists of a large depolarization of a group of neurons with action potentials, as indicated by the vertical lines on the large depolarization. The PDS is followed by repolarization. The PDS and repolarization corresponds to a spike and wave on the EEG. A seizure occurs when there is a massive depolarization of cells without intervening periods of repolarization. This would correspond to the tonic phase of the seizure. As inhibition increases during the seizure, there is a cycle of PDS followed by repolarization. This corresponds to the clonic phase of the seizure



J. Perkins  
MS, MFA, CMI

**B.** Examples of molecular targets of antiepileptic drugs that reduce excitability. This may occur through blockage of calcium, sodium, and potassium channels or through reducing ion flow through NMDA and AMPA receptors. Levetiracetam binds to synaptic vesicles, which may lead to reduced neurotransmitter release.

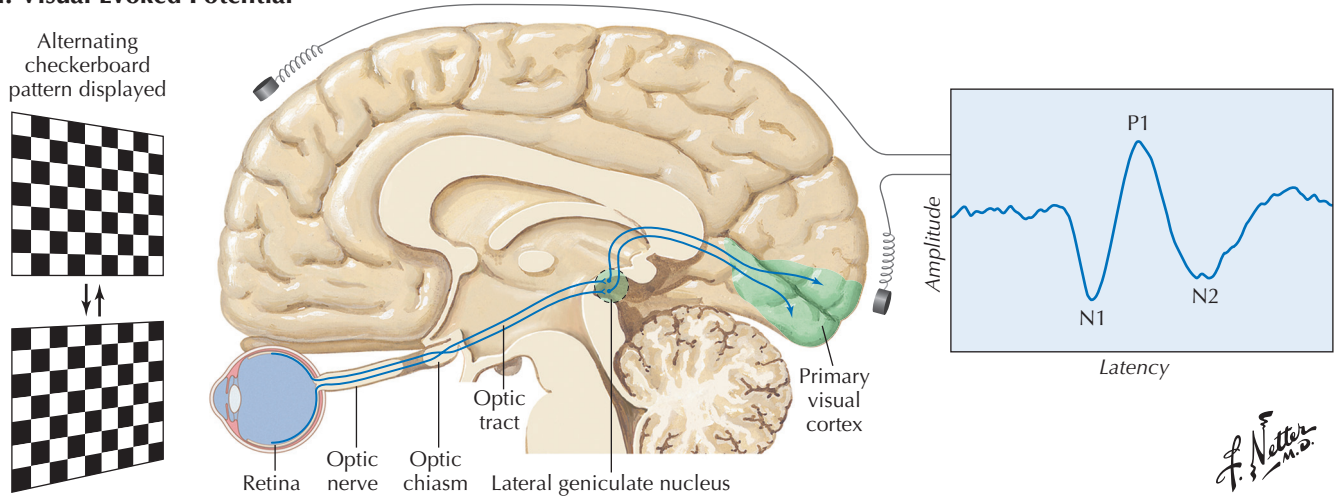


**C.** Examples of molecular targets of antiepileptic drugs that enhance inhibition. Drugs may increase amount of GABA postsynaptically by blocking GABA uptake or increase intracellular GABA by reducing degradation of GABA. Enhancing chloride flow through the GABA receptor is a common mechanism of inhibitory drugs, such as barbiturates and benzodiazepines. Levetiracetam displaces zinc from the GABA receptor, which results in increased chloride currents.

### 1.30 TYPES OF ELECTRICAL DISCHARGES IN GENERALIZED SEIZURES AND SITES OF ACTION OF ANTISEIZURE MEDICATIONS

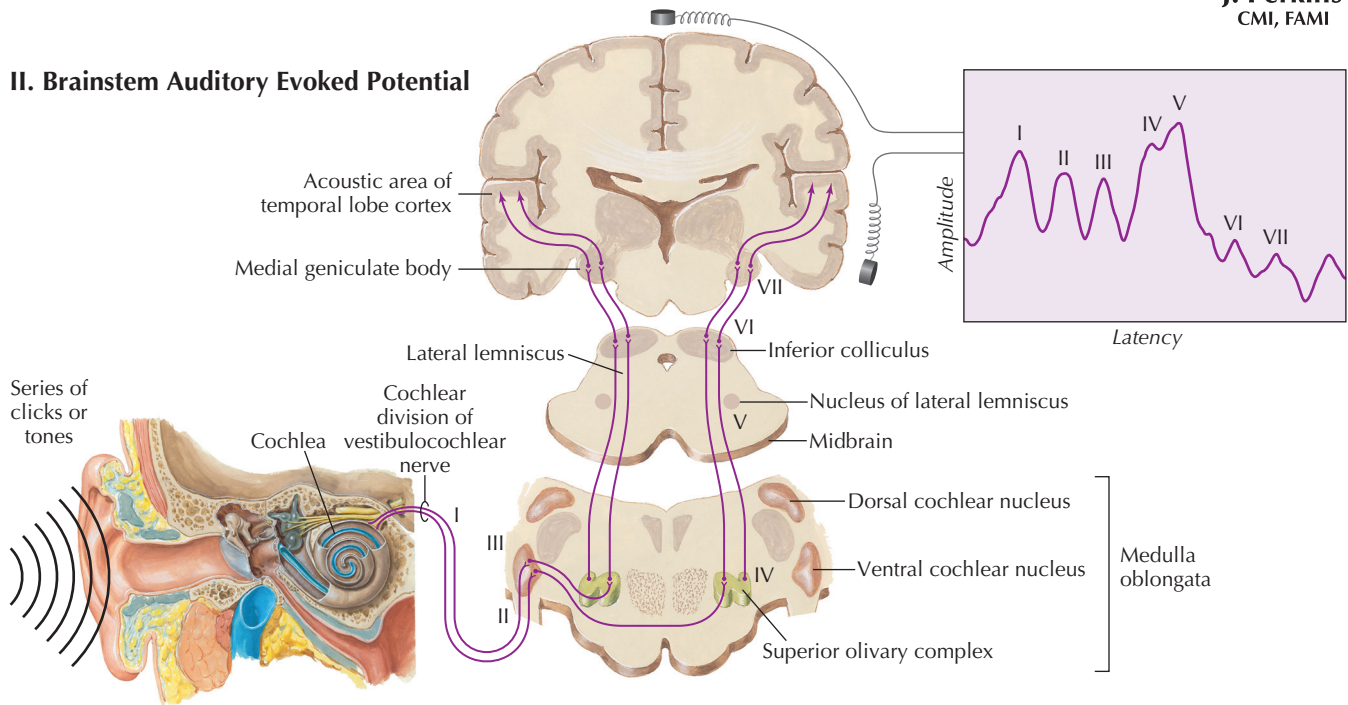
Illustrations of types of electrical discharges in generalized seizures and the sites of action for antiseizure medications that reduce excitability or that enhance inhibition.

## I. Visual Evoked Potential



*J. Netter M.D.*  
**J. Perkins**  
 CMI, FAMI

## II. Brainstem Auditory Evoked Potential

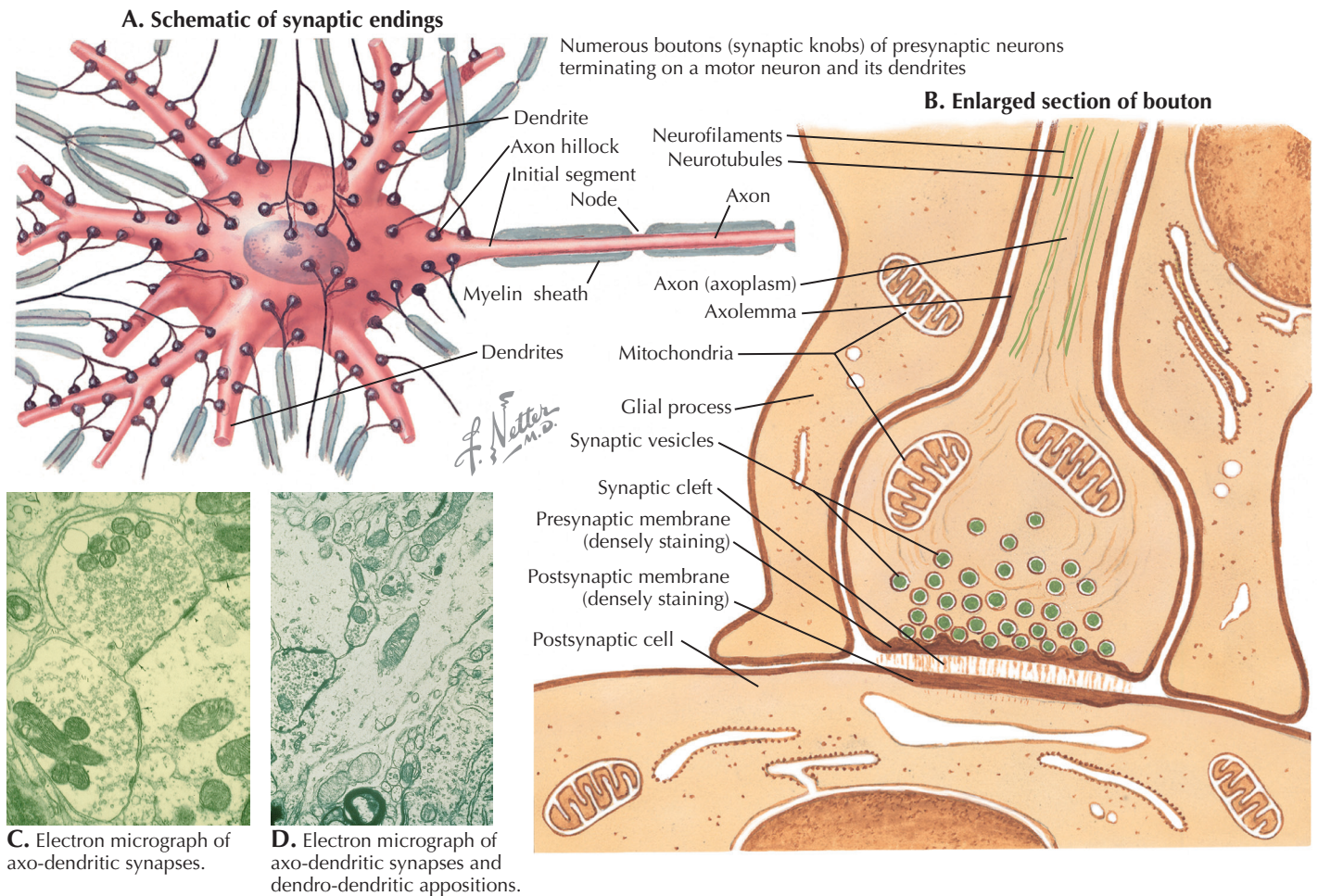


### 1.31 VISUAL AND AUDITORY EVOKED POTENTIALS

Electrophysiological recordings can be used to evaluate the intactness of specific sensory systems, including the visual system and the auditory system. *I. Visual evoked potentials.* The visual stimulus is often an alternating flashing checkerboard (2 Hz), with recording done over the primary visual cortex in the midline. The normal latencies for recordings are 70 msec for N1 (negative 1), 100 msec for P1 (positive 1), and 140 msec for N2 (negative 2). Damage to the retino-geniculo-

calcarine pathway may result in altered latencies and amplitudes. *II. Brainstem auditory evoked responses or potentials (BAER).* The auditory stimulus is a series of clicks or tones, with recording done over the temporal lobe auditory cortex. Seven distinctive peak latencies occur: I. distal auditory nerve; II. proximal auditory nerve; III. cochlear nuclei; IV. superior olivary complex; V. nucleus of the lateral lemniscus; VI. inferior colliculus; and VII. medial geniculate nucleus. Altered latencies and amplitudes may indicate damage or disruption to the auditory pathway at specific sites.





## NEUROTRANSMITTER AND SIGNALING PROPERTIES

### 1.32 SYNAPTIC MORPHOLOGY

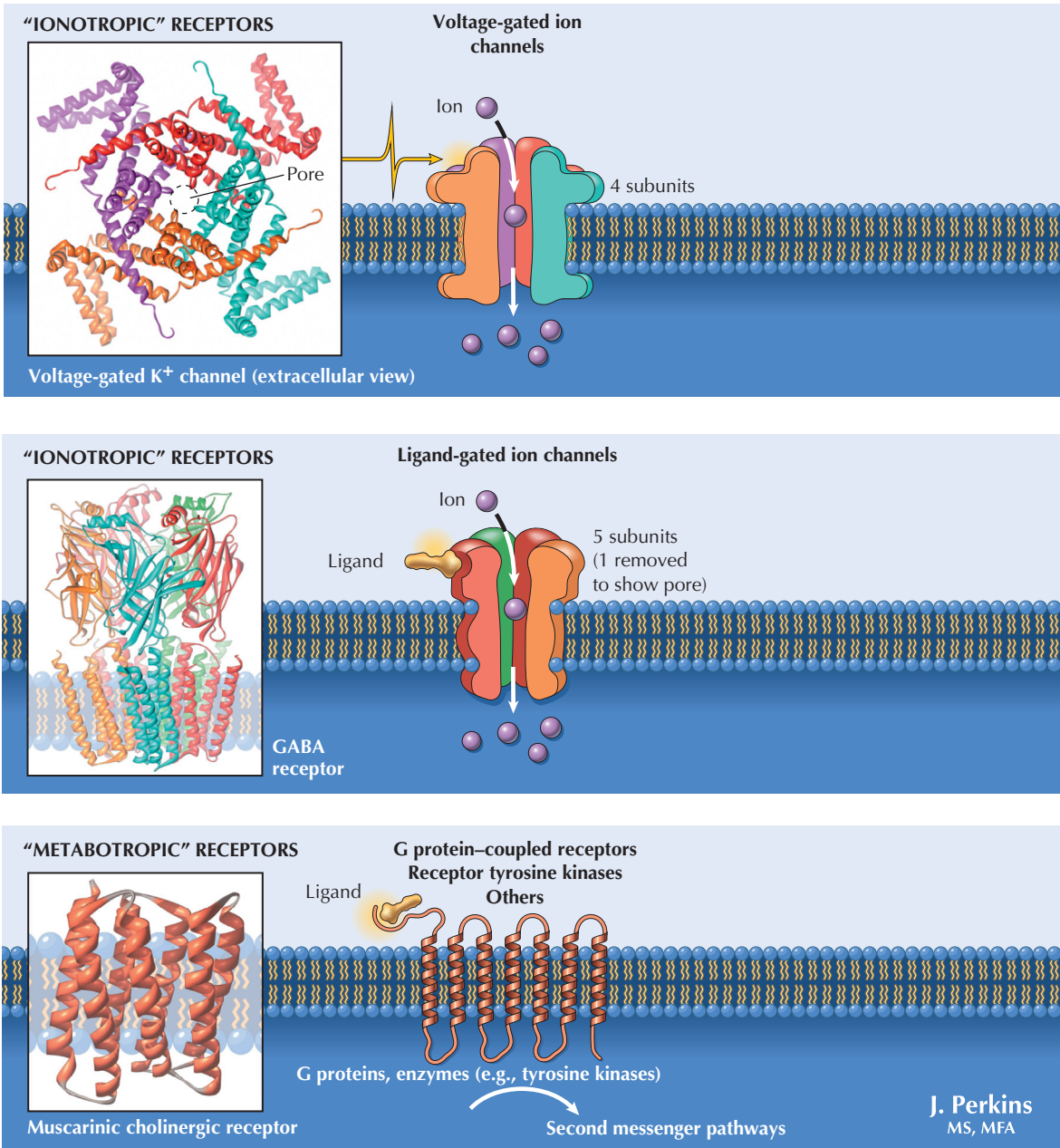
Synapses are specialized sites where neurons communicate with each other and with effector or target cells. **A**, A typical neuron that receives numerous synaptic contacts on its cell body and associated dendrites. The contacts are derived from both myelinated and unmyelinated axons. Incoming myelinated axons lose their myelin sheaths, exhibit extensive branching, and terminate as synaptic boutons (terminals) on the target (in this example, motor) neuron. **B**, An enlargement of an axosomatic terminal. Chemical neurotransmitters are packaged in synaptic vesicles. When an action potential invades the terminal region, depolarization triggers  $\text{Ca}^{2+}$  influx into the terminal, causing numerous synaptic vesicles to fuse with the presynaptic membrane, releasing their packets of neurotransmitter into the synaptic cleft. The neurotransmitter can bind to receptors on the postsynaptic membrane, resulting in graded excitatory or inhibitory postsynaptic potentials or in neuromodulatory effects on intracellular signaling systems in the target cell. There is sometimes a mismatch between the site of release of a neurotransmitter and the location of target neurons possessing receptors for the neurotransmitter (can be immediately adjacent or at a distance). Many nerve terminals can release multiple neurotransmitters; the

process is regulated by gene activation and by the frequency and duration of axonal activity. Some nerve terminals possess presynaptic receptors for their released neurotransmitters. Activation of these presynaptic receptors regulates neurotransmitter release. Some nerve terminals also possess high-affinity uptake carriers for transport of the neurotransmitters (e.g. dopamine, norepinephrine, serotonin) back into the nerve terminal for repackaging and reuse.

#### CLINICAL POINT

Synaptic endings, particularly axodendritic and axosomatic endings, terminate abundantly on some neuronal cell types such as LMNs. The distribution of synapses, based on a hierarchy of descending pathways and interneurons, orchestrates the excitability of the target neuron. If one of the major sources of input is disrupted (such as the corticospinal tract in an internal capsule lesion, which may occur in an ischemic stroke) or if damage has occurred to the collective descending UMN pathways (as in a spinal cord injury), the remaining potential sources of input can sprout and occupy regional sites left bare because of the degeneration of the normal complement of synapses. As a result, primary sensory inputs from Ia afferents and other sensory influences, via interneurons, can take on a predominant influence over the excitability of the target motor neurons, leading to a hyperexcitable state. This may account in part for the hypertonic state and hyperreflexic responses to stimulation of primary muscle spindle afferents (muscle stretch reflex) and of flexor reflex afferents (nociceptive stimulation). Recent studies indicate that synaptic growth, plasticity, and remodeling can continue into adulthood and even into old age.

CENTRAL NERVOUS SYSTEM NEUROTRANSMITTERS, RECEPTORS, AND DRUG TARGETS



Select CNS Neurotransmitters and Neuromodulators

Acetylcholine  
Adenosine  
AMP, ADP, ATP  
Anandamide  
Aspartate  
Bombesin  
Bradykinin  
Calcitonin gene-related peptide (CGRP)  
Cholecystokinin  
Cytokines

Dopamine  
Eicosanoids  
Endothelins  
Epinephrine  
FMRF-amide-related peptides  
GABA  
Galanin  
Gastrin  
Glutamate  
Glutamine

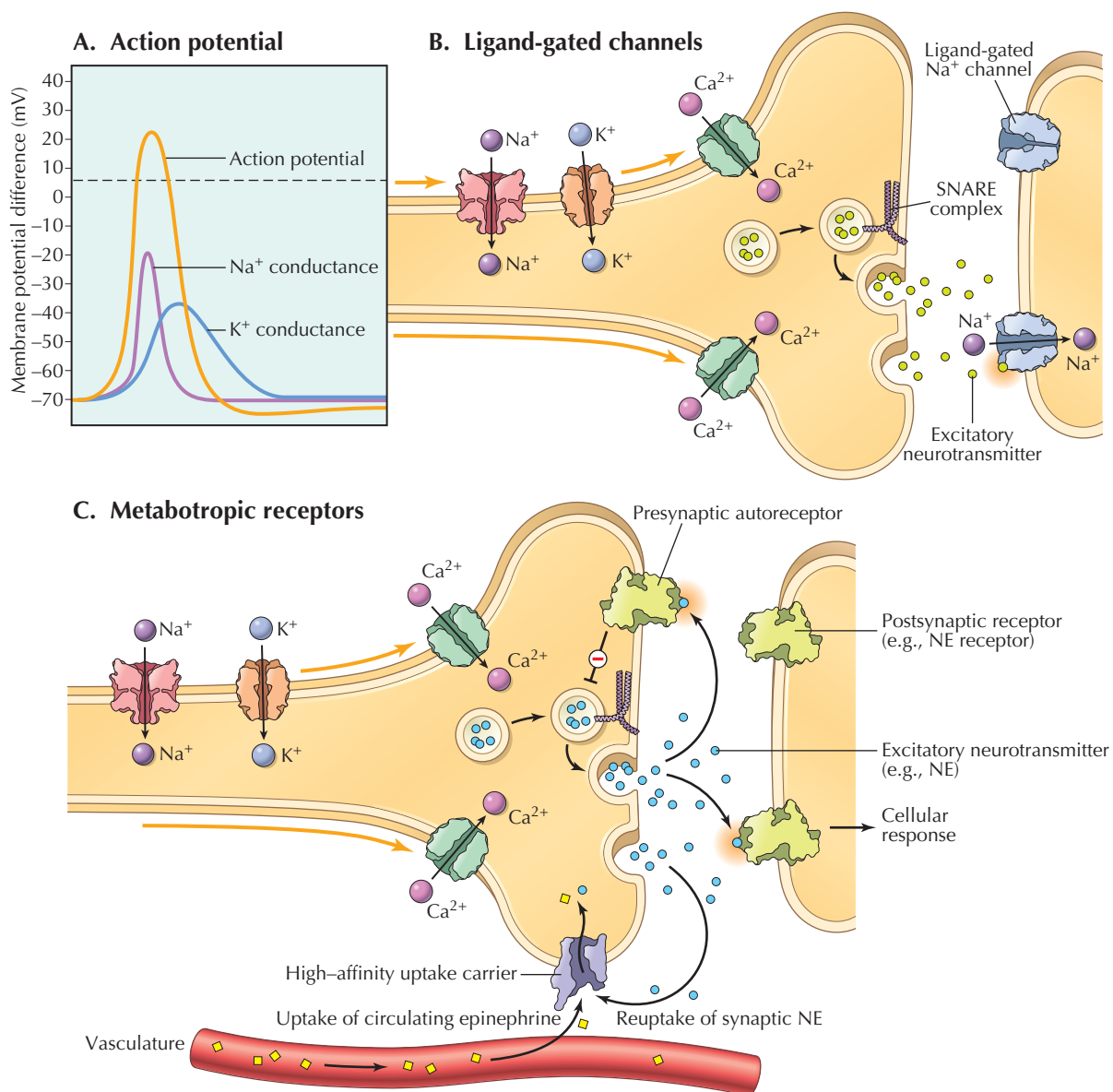
Glycine  
Histamine  
Neuropeptide Y  
Neurosteroids  
Neurotensin  
NO (nitric oxide)  
Norepinephrine  
Opioid peptides (endorphins, enkephalins, dynorphins)

Oxytocin  
Somatostatin  
Substance P (tachykinins)  
Taurine  
Vasoactive intestinal polypeptide (VIP)  
Vasopressin

1.33 MECHANISMS OF MOLECULAR SIGNALING IN NEURONS

Types of molecular signaling in neurons are shown, including ionotropic receptors (both voltage-gated ion channels and ligand-gated channels) and metabotropic receptors.





### 1.34 NEUROTRANSMITTER RELEASE

**A**, Major ion conductances are triggered by an action potential (AP). **B**, Their effects on neurotransmitter (NT) release as related to ligand-gated channels influencing postsynaptic excitability. NT is packaged in synaptic vesicles; these vesicles, in response to nerve terminal depolarization and  $\text{Ca}^{2+}$  influx, merge with the nerve terminal membrane through a mechanism involving the SNARE complex. Through this mechanism of docking proteins, membrane fusion, and NT exocytosis, multiple vesicles simultaneously release their NT content, called *quantal release*, allowing postsynaptic stimulation. SNARE proteins represent a large superfamily of soluble NSF (N-ethylmaleimide-sensitive factor) attachment protein receptors that are composed of four alpha helices that mediate vesicle fusion and exocytosis.

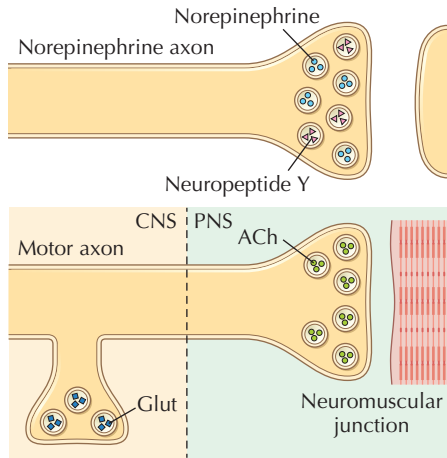
**C**, Metabotropic receptors responding to nerve terminal depolarization with SNARE complex-mediated vesicle membrane fusion and exocytosis. Both postsynaptic and presynaptic receptors bind with NT (in this case norepinephrine, NE) and transduce the receptor-ligand binding into intracellular signaling. The presynaptic receptor can modulate nerve ter-

minal excitability and subsequent NT release. The postsynaptic receptor can modulate postsynaptic excitability and the postsynaptic membrane responsiveness to other NTs. High-affinity uptake carriers remove NE from the synaptic cleft back into the nerve terminal for repackaging into synaptic vesicles. This NE uptake carrier also can take up epinephrine (E) from the circulation. Uptaken E also is repackaged into the NE synaptic vesicles and is preferentially released on subsequent nerve terminal depolarization. This E substitute-NT mechanism provides augmented receptor activation (especially beta receptor activation by E) during sympathetic responses.

#### CLINICAL POINT

Botulinum toxin (BOTOX) is a proteolytic enzyme that cleaves SNARE proteins in nerve terminals, preventing vesicle fusion with the nerve terminal membrane and release of NT. Hence, nerve APs do not result in NT release; for muscles targeted by cholinergic motor end plates, botulinum toxin results in muscle paralysis. Deliberate clinical use of this toxin can alleviate muscle spasm in spasmodic torticollis, dystonia, and other conditions of excess chronic muscle contraction. This toxin is also used cosmetically to reduce or eliminate the appearance of facial skin wrinkles through selective paralysis of facial muscles.

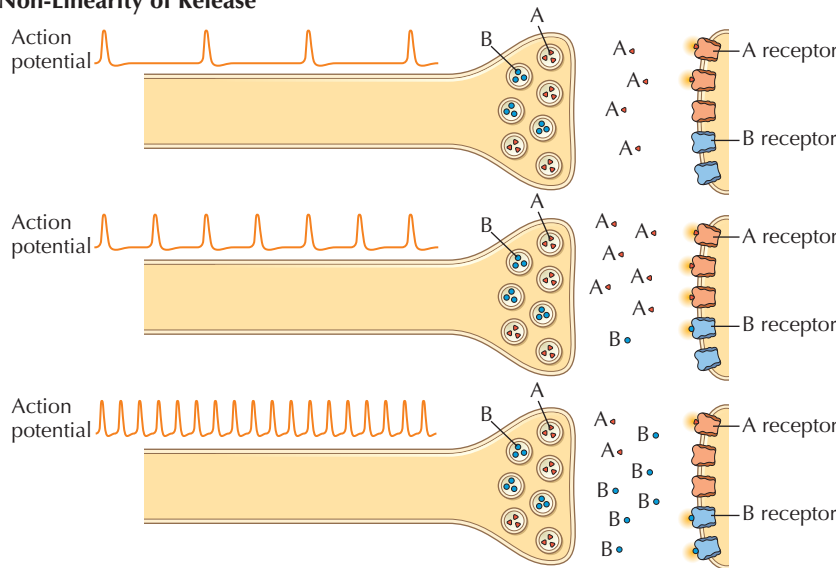
### Co-Localization and Release



Neurotransmitter	Cotransmitters
DA	Glutamate, neurotensin, CCK or multiples + calbindin
NE (sympathetics)	Neuropeptide Y, somatostatin
NE (locus coeruleus)	Galanin
SP	CGRP (calcitonin gene-related peptide)
Serotonin (5-HT)	Glutamate, GABA
CRF	GABA
GHRH	DA, GABA
ACh	VIP
Met-enkephalin	Oxytocin (in magnocellular neurons of hypothalamus)

Fiber Type	Colocalized neurotransmitters
Motor axon	ACh at neuromuscular junction, glutamate in SC
Medial habenula	ACh, glutamate
Arcuate nucleus	DA, GABA, many others
Mossy fibers	GABA, glycine
Dorsal horn neurons	Met-enkephalin, GABA
Striatal neurons	Met-enkephalin, GABA

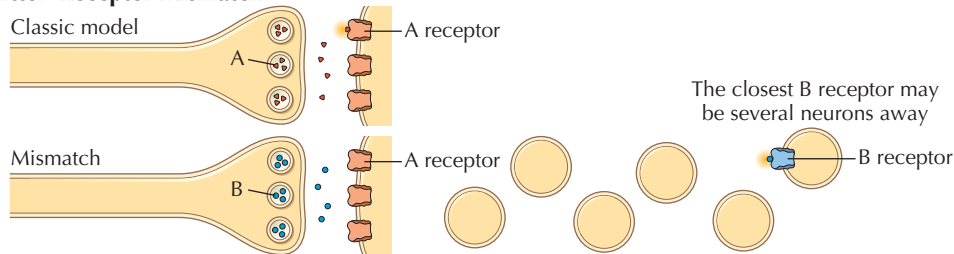
### Non-Linearity of Release



**J. Perkins**  
CMI, FAMI

Diminishing release at high frequency due to:  
1. Depletion of vesicles  
2. Depletion of extra-cellular  $Ca^{2+}$

### Neurotransmitter-Receptor Mismatch

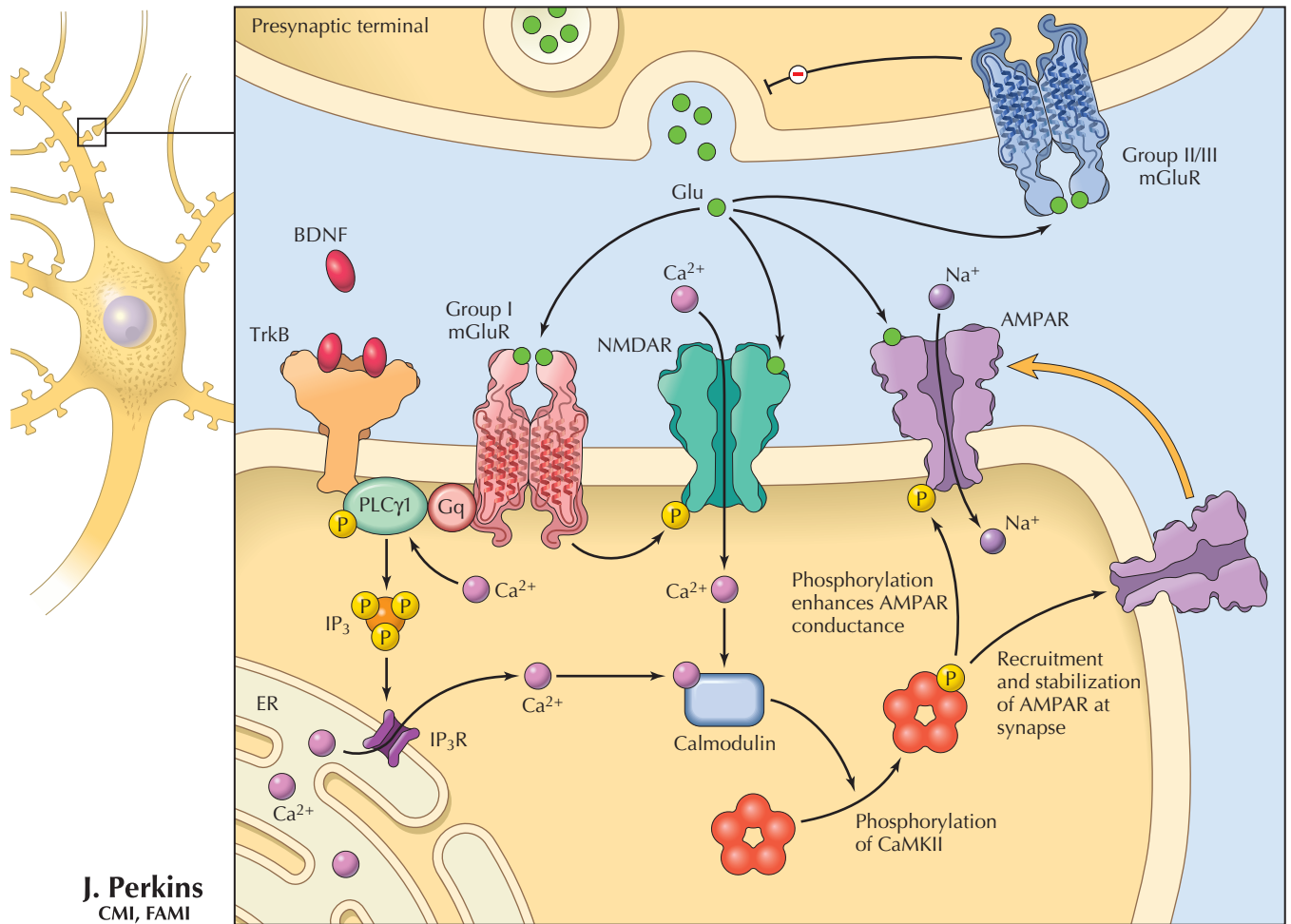


## 1.35 MULTIPLE NEUROTRANSMITTER SYNTHESIS, RELEASE, AND SIGNALING FROM INDIVIDUAL NEURONS

Many, perhaps most, nerve terminals co-localize and release multiple neurotransmitters (NT), each presumably packaged in its own synaptic vesicles. Major co-localized NTs, sorted by transmitter and by fiber type, are presented in the table. Some authors have noted as many as seven or more NTs present in a single type of nerve terminal. It should be noted that some NTs are present in the presynaptic cytoplasm and are not released by quantal (vesicle-based) release. Some NTs are packaged in vesicles in the cell body and transported by axonal transport (e.g., neuropeptides), while other NTs are synthesized and/or packaged locally in the nerve terminals (e.g., amino acids, monoamines).

NT release is usually nonlinear, with some NTs diminishing their quantal release at higher action potential (AP) frequencies, while other co-localized NTs (especially some neuropeptides) are released only at much higher AP frequencies. A further phenomenon affecting the functional consequence of NT release is the frequent NT-receptor mismatch. Some NTs are released into a synaptic cleft and immediately activate receptors on the postsynaptic site (e.g., ACh at the neuromuscular junction). However, some NTs, when released, have no local receptors with which to interact, except at distant sites. Hence, NT-receptor activation in these circumstances may occur only during particularly robust or prolonged NT transmitter release.

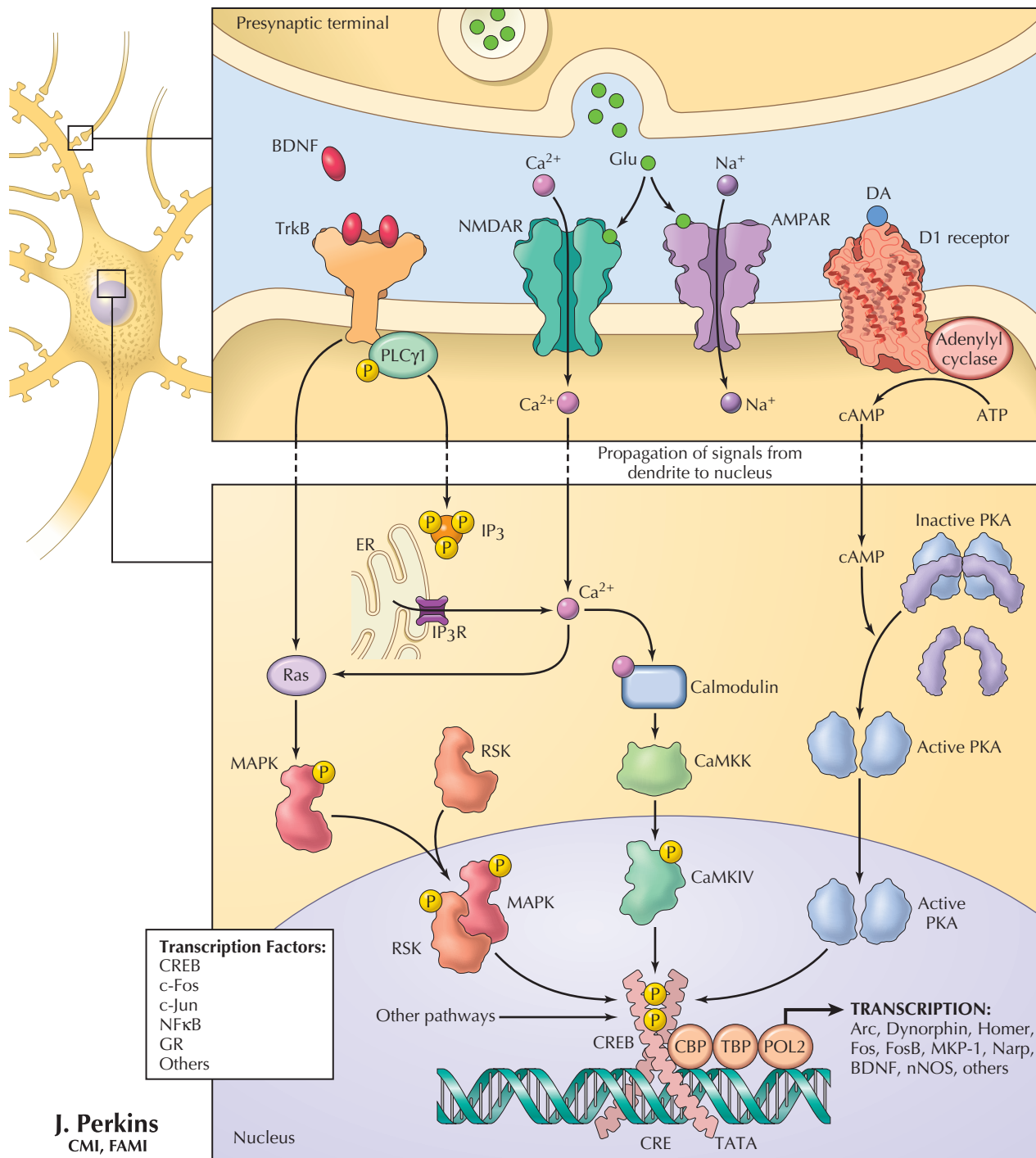




### 1.36 NEURONAL SIGNAL TRANSDUCTION: LOCAL REGULATION OF SYNAPTIC STRENGTH AT AN EXCITATORY SYNAPSE

Glutamate released at excitatory synapses can bind to several different classes of receptors including ligand regulated ion channels for sodium ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AMPAR) and calcium (*N*-methyl-D-aspartate receptor; NMDAR), as well as several types of G-protein coupled metabotropic glutamate receptors (mGluRs). Repeated firing at such synapses results in modulation of synaptic strength through several mechanisms, including increased levels of the second messenger  $\text{Ca}^{+2}$  via NMDAR, which enhances AMPAR action by activation of a calcium-calmodulin kinase II (CaMKII) dependent pathway resulting in AMPAR phosphorylation and increased AMPAR recruit-

ment and stabilization. Group I mGluR are generally found on postsynaptic sites and can further increase synaptic strength by Gq-mediated activation of phospholipase C gamma 1 (PLCγ1), leading to production of inositol 1,4,5-triphosphate (IP3) and release of calcium from endoplasmic reticulum (ER) stores by activation of the inositol 1,4,5-triphosphate receptor (IP3R). In contrast, groups II and III mGluRs, which are typically present on presynaptic sites, lead to decreased release of glutamate via their G-protein coupled second messengers, resulting in feedback inhibition of the process. Other factors such as brain-derived neurotrophic factor (BDNF) can modulate glutamatergic signaling by activating tropomyosin receptor kinase B (TrkB), resulting in activation of PLCγ1 and IP3-dependent calcium release from the ER.

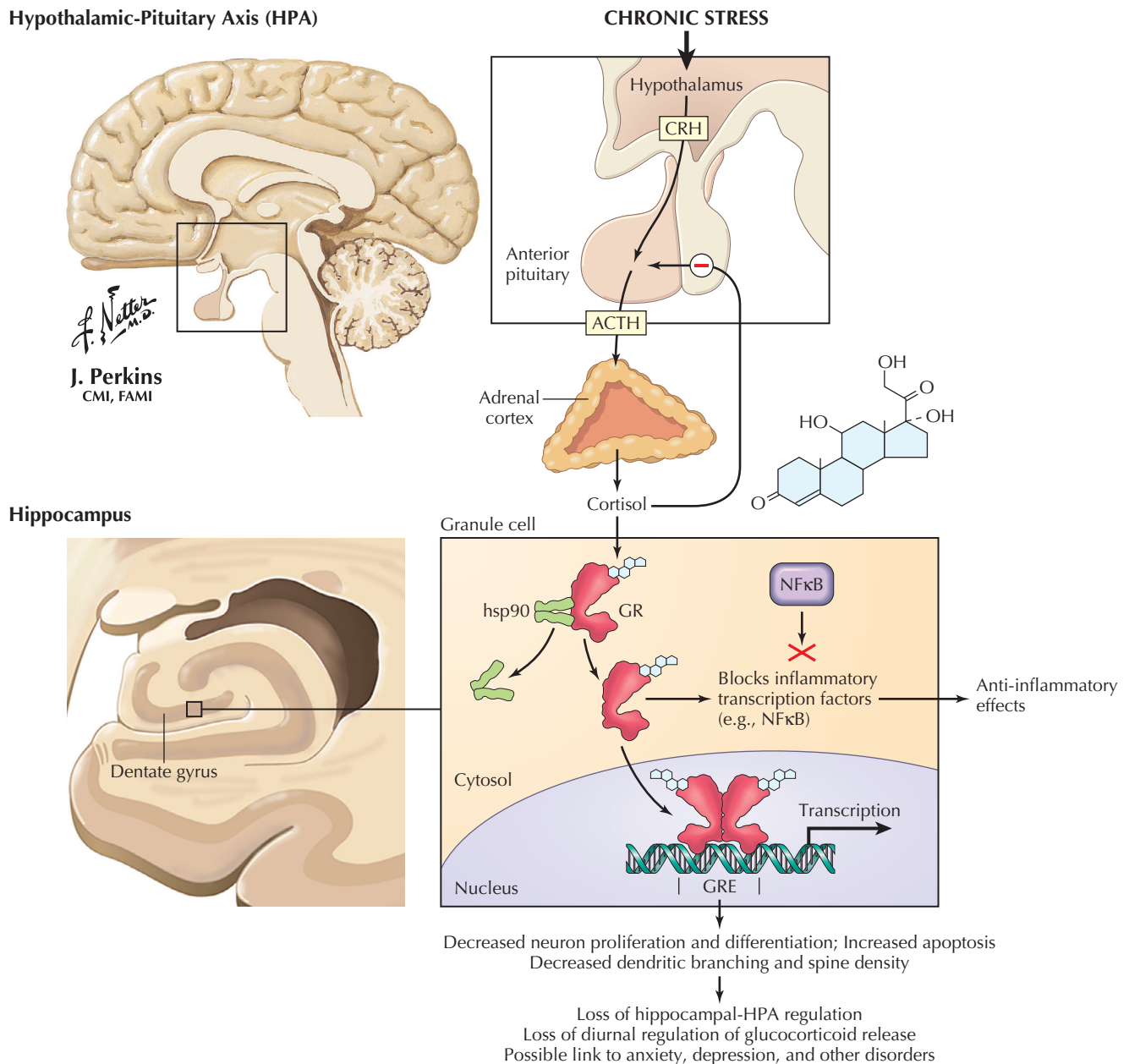


### 1.37 NEURONAL SIGNAL TRANSDUCTION: REGULATION OF NUCLEAR SIGNALING

In addition to short-term modulation of individual synapses, increased excitatory neuron firing can lead to changes in gene expression through several mechanisms. In particular, increased calcium levels arising from NMDAR activation and BDNF binding to TrkB can activate calcium calmodulin kinase IV (CaMKIV), leading to phosphorylation and activation of the cAMP response element-binding protein (CREB) transcription factor, which recruits critical transcriptional elements such as CREB-binding protein (CBP), TATA-binding protein (TBP), and RNA polymerase II (POL2) to genes with cAMP response elements (CRE), ultimately leading to tran-

scription of factors related to synaptic plasticity. CREB can also be phosphorylated by cAMP-dependent activation of protein kinase A (PKA), providing a mechanism for modulation of gene transcription by G-protein coupled receptors such as dopamine 1-like receptors (D1 receptor). Activation of growth factor receptors such as TrkB can also result in Ras-dependent activation of the mitogen activated protein kinase (MAPK) pathway, ultimately leading to phosphorylation of CREB by a MAPK/ribosomal s6 kinase (RSK) dimer. In addition to CREB, many other transcription factors can be activated to influence neuronal gene expression including c-Fos, c-Jun, nuclear factor kappa B (NF- $\kappa$ B), and steroid hormone receptors such as the glucocorticoid receptor (GR; see Fig. 1.38).

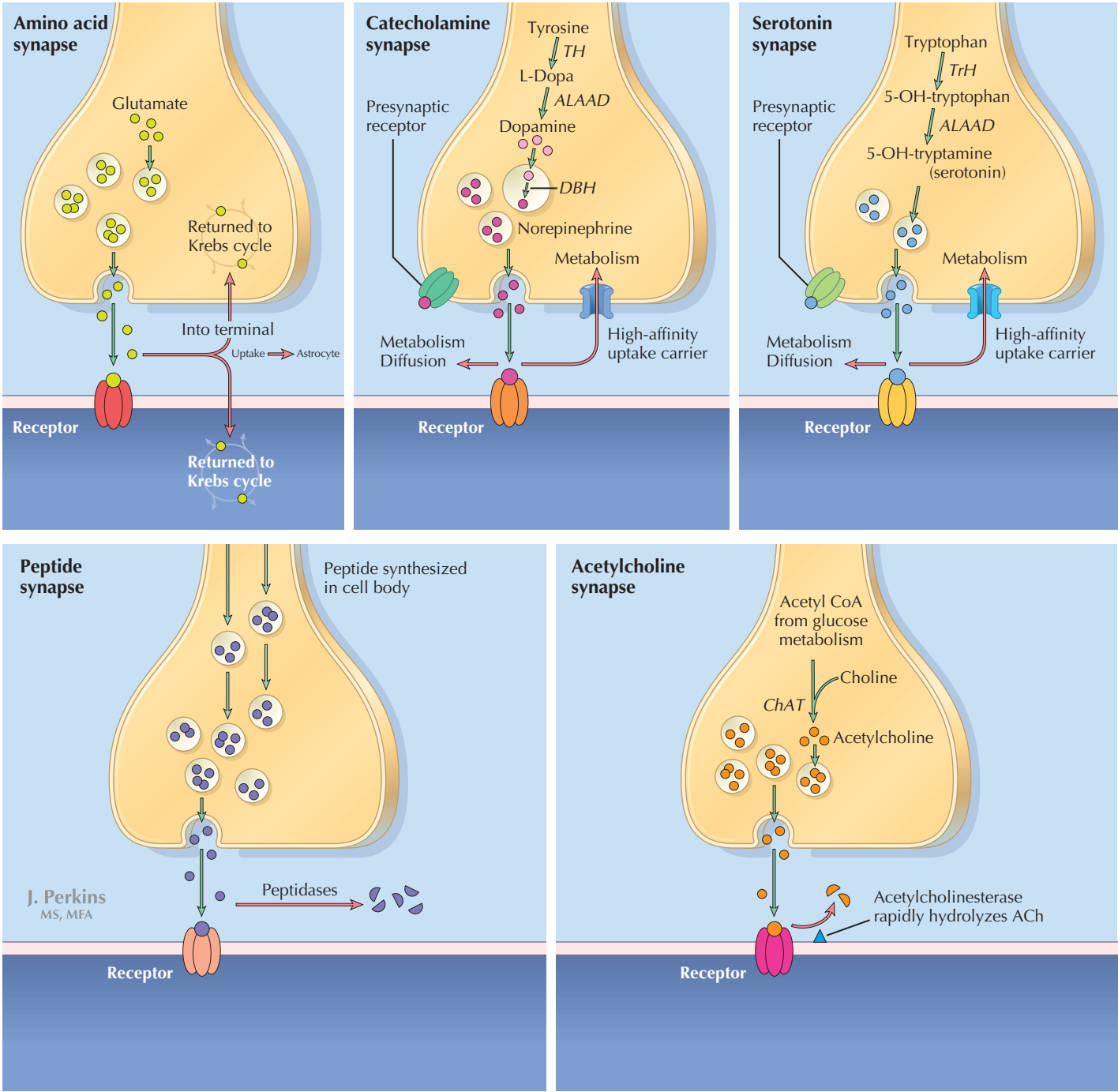
## Hypothalamic-Pituitary Axis (HPA)



### 1.38 GLUCOCORTICOID REGULATION OF NEURONS AND APOPTOSIS

Glucocorticoid production is controlled by the hypothalamic-pituitary-adrenal (HPA) axis in which hypothalamic corticotropin releasing hormone (CRH) stimulates cells in the anterior pituitary via the hypophyseal-portal circulation to produce adrenocorticotrophic hormone (ACTH). ACTH, in turn, stimulates the adrenal cortices to produce the glucocorticoid hormone cortisol. Cortisol interacts with glucocorticoid receptors (GR) in the cytoplasm of some neurons to effect dissociation from chaperone proteins such as heat shock protein (hsp) 90 and translocation to the nucleus, where the activated GR interacts with glucocorticoid response elements (GRE) to effect gene transcription. Cortisol acts on many body tissues to promote metabolic and antiinflammatory effects, in the latter case by blocking inflammatory transcription factors such as nuclear factor  $\kappa$ B (NF- $\kappa$ B). Under normal

conditions, the HPA axis is regulated by feedback at several levels, including regulation of CRH release via the hippocampus, resulting in normal diurnal regulation of systemic cortisol levels. In the hippocampus, low to moderate levels of cortisol provide optimal memory acquisition and consolidation by supporting synaptic plasticity. However, under conditions of chronic stress, sustained high levels of cortisol can negatively affect hippocampal neurons, particularly the granule cells of the dentate gyrus, resulting in decreased neurogenesis, decreased dendritic complexity, and cell death via apoptosis. Hippocampal cell loss and dysfunction can lead to loss of hippocampal control over cortisol release, resulting in loss of normal diurnal release patterns, which is seen in old age and in diseases such as Alzheimer's. Such changes have also been linked to psychiatric disorders. Loss of diurnal cortisol rhythms also contributes to metabolic dysfunction and truncal obesity in the periphery.



Chemical Neurotransmission



### 1.39 CHEMICAL NEUROTRANSMISSION

#### AMINO ACID SYNAPSE

Amino acids used by a neuron as neurotransmitters are compartmentalized for release as neurotransmitters in synaptic vesicles. The amino acid glutamate (depicted in this diagram) is the most abundant excitatory neurotransmitter in the CNS. Following release from synaptic vesicles, some glutamate binds to postsynaptic receptors. Released glutamate is inactivated by uptake into both pre- and postsynaptic neurons, where the amino acid is incorporated into the Krebs cycle or reused for a variety of functions. Glutamate also is taken up and recycled in the CNS by astrocytes.

#### CATECHOLAMINE SYNAPSE

Catecholamines are synthesized from the dietary amino acid tyrosine, which is taken up competitively into the brain by a carrier system. Tyrosine is synthesized into L-dopa by tyrosine hydroxylase (TH), the rate-limiting synthetic enzyme. Additional conversion into dopamine takes place in the cytoplasm via aromatic L-amino acid decarboxylase (ALAAD). Dopamine is taken up into synaptic vesicles and stored for subsequent release. In noradrenergic nerve terminals, dopamine beta-hydroxylase (DBH) further hydroxylates dopamine into norepinephrine in the synaptic vesicles. In adrenergic nerve terminals, norepinephrine is methylated to epinephrine by phenylethanolamine N-methyl transferase (PNMT). Following release, the catecholamine neurotransmitter binds to appropriate receptors (dopamine and alpha- and beta-adrenergic receptors) on the postsynaptic membrane, altering postsynaptic excitability, second-messenger activation, or both. Catecholamines also can act on presynaptic receptors, modulating the excitability of the presynaptic terminal and influencing subsequent neurotransmitter release. Catecholamines are inactivated by presynaptic reuptake (high-affinity uptake carrier) and, to a lesser extent, by metabolism (monoamine oxidase deamination and catechol-O-methyltransferase) and diffusion.

#### SEROTONIN SYNAPSE

Serotonin is synthesized from the dietary amino acid tryptophan, taken up competitively into the brain by a carrier system. Tryptophan is synthesized to 5-hydroxytryptophan (5-OH-tryptophan) by tryptophan hydroxylase (TrH), the rate-limiting synthetic enzyme. Conversion of 5-hydroxytryptophan to 5-hydroxytryptamine (5-HT, serotonin) takes place in the cytoplasm by means of ALAAD. Serotonin is stored in synaptic vesicles. Following release, serotonin can bind to receptors on the postsynaptic membrane, altering postsynaptic excitability, second messenger activation, or both. Serotonin also can act on presynaptic receptors (5-HT receptors), modulating

the excitability of the presynaptic terminal and influencing subsequent neurotransmitter release. Serotonin is inactivated by presynaptic reuptake (high-affinity uptake carrier) and to a lesser extent by metabolism and diffusion.

#### PEPTIDE SYNAPSES

Neuropeptides are synthesized from prohormones, large peptides synthesized in the cell body from mRNA. The larger precursor peptide is cleaved posttranslationally to active neuropeptides, which are packaged in synaptic vesicles and transported anterogradely by the process of axoplasmic transport. These vesicles are stored in the nerve terminals until released by appropriate excitation-secretion coupling induced by an action potential. The neuropeptide binds to receptors on the postsynaptic membrane. In the CNS, there is often an anatomic mismatch between the localization of peptidergic nerve terminals and the localization of cells possessing membrane receptors responsive to that neuropeptide, suggesting that the amount of release and the extent of diffusion may be important factors in neuropeptide neurotransmission. Released neuropeptides are inactivated by peptidases.

#### ACETYLCHOLINE (CHOLINERGIC) SYNAPSE

Acetylcholine (ACh) is synthesized from dietary choline and acetyl coenzyme A (CoA), derived from the metabolism of glucose by the enzyme choline acetyltransferase (ChAT). ACh is stored in synaptic vesicles; following release, it binds to cholinergic receptors (nicotinic or muscarinic) on the postsynaptic membrane, influencing the excitability of the postsynaptic cell. Enzymatic hydrolysis (cleavage) by acetylcholine esterase rapidly inactivates ACh.

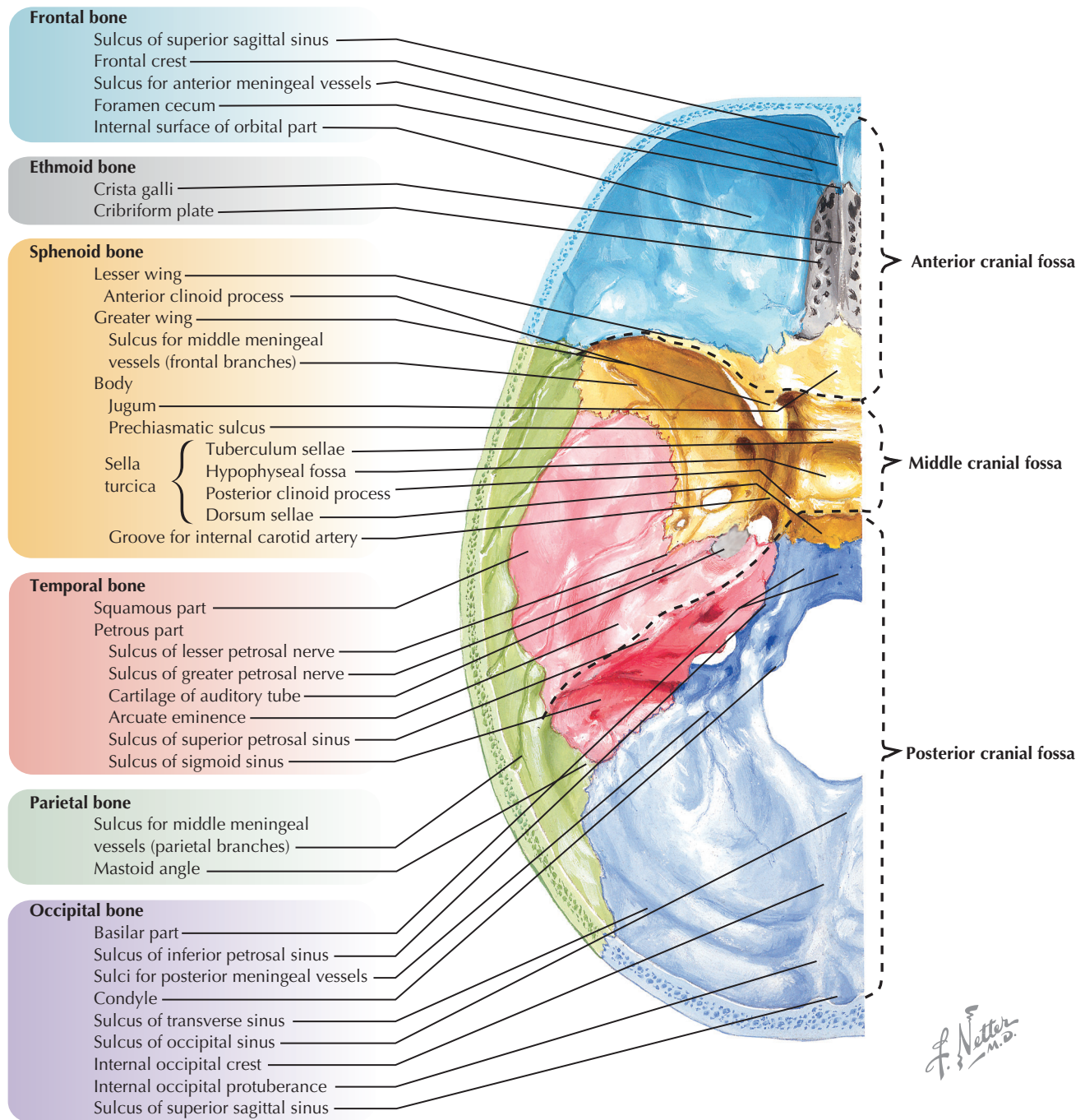
#### CLINICAL POINT

Synthesis of catecholamines in the brain is rate limited by the availability of the precursor amino acid tyrosine; synthesis of serotonin, an indoleamine, is rate limited by the availability of the precursor amino acid tryptophan. Tyrosine and tryptophan compete with other amino acids—phenylalanine, leucine, isoleucine, and valine—for uptake into the brain through a common carrier mechanism. When a good protein source is available in the diet, tyrosine is present in abundance, and robust catecholamine synthesis occurs; when a diet lacks sufficient protein, tryptophan is competitively abundant compared with tyrosine, and serotonin synthesis is favored. This is one mechanism by which the composition of the diet can influence the synthesis of serotonin as opposed to catecholamine and influence mood and affective behavior. During critical periods of development, if low availability of tyrosine occurs because of protein malnourishment, central noradrenergic axons cannot exert their trophic influence on cortical neuronal development such as the visual cortex; stunted dendritic development occurs, and the binocular responsiveness of key cortical neurons is prevented. Thus, nutritional content and balance are important to both proper brain development and ongoing affective behavior.

# 2

## SKULL AND MENINGES

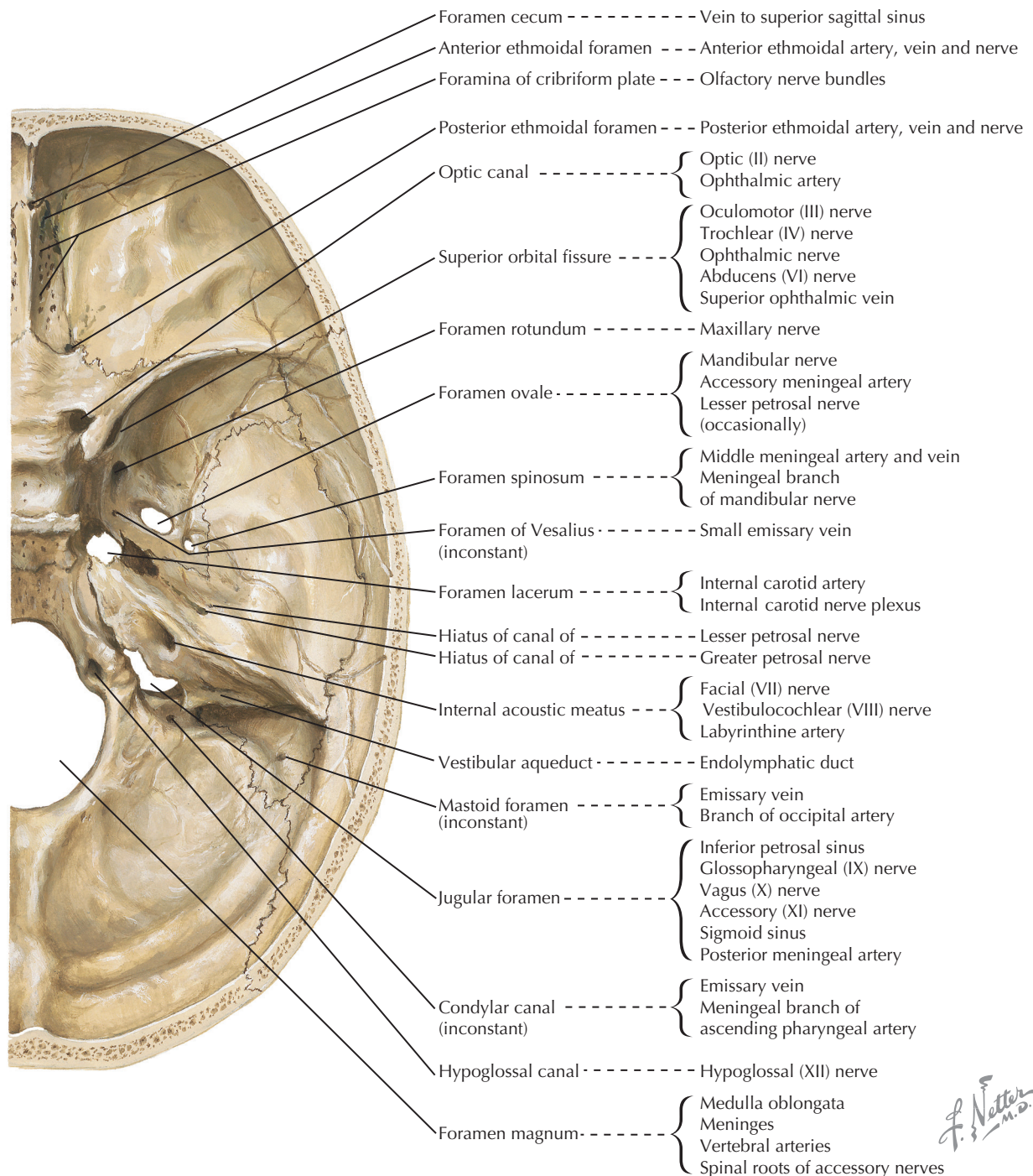
- 2.1 Interior View of the Base of the Adult Skull
- 2.2 Foramina in the Base of the Adult Skull
- 2.3 Bony Framework of the Head and Neck
- 2.4 Schematic of the Meninges and Their Relationships to the Brain and Skull
- 2.5 Hematomas



## 2.1 INTERIOR VIEW OF THE BASE OF THE ADULT SKULL

The anterior, middle, and posterior cranial fossae house the anterior frontal lobe, temporal lobe, and cerebellum and brain stem, respectively. The fossae are separated from each other by bony structures and dural membranes. A swelling of the

brain or the presence of mass lesions can selectively exert pressure within an individual fossa. The perforated cribriform plate allows the olfactory nerves to penetrate into the olfactory bulb, a site where head trauma can result in the tearing of the penetrating olfactory nerve fibers.



*F. Netter M.D.*

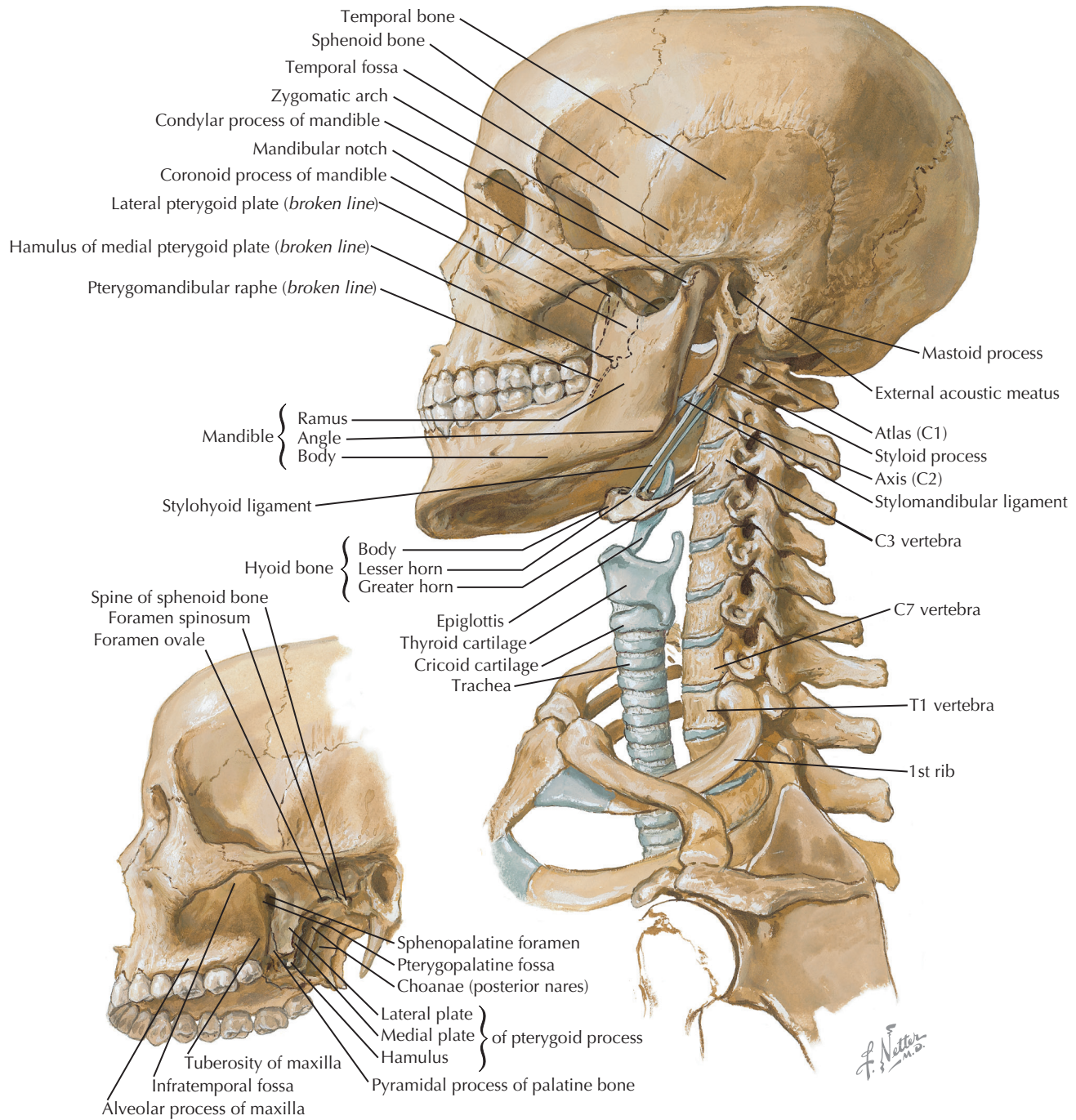
## 2.2 FORAMINA IN THE BASE OF THE ADULT SKULL

The foramina in the base of the skull allow major nerves and blood vessels to course through the skull. Pressure, traction, and masses can damage structures traversing these small spaces that snugly confine the structures.

### CLINICAL POINT

The foramina of the skull are narrow openings that allow the passage of nerves and blood vessels. Under normal circumstances, there is enough room for comfortable passage of these structures without traction or pressure. However, with the presence of a tumor at a foramen, the passing structures can be compressed or damaged. For example, a tumor at the internal acoustic meatus can result in ipsilateral facial and vestibuloacoustic nerve damage, and a tumor at the jugular foramen can result in damage to the glossopharyngeal, vagus, and spinal accessory nerves.

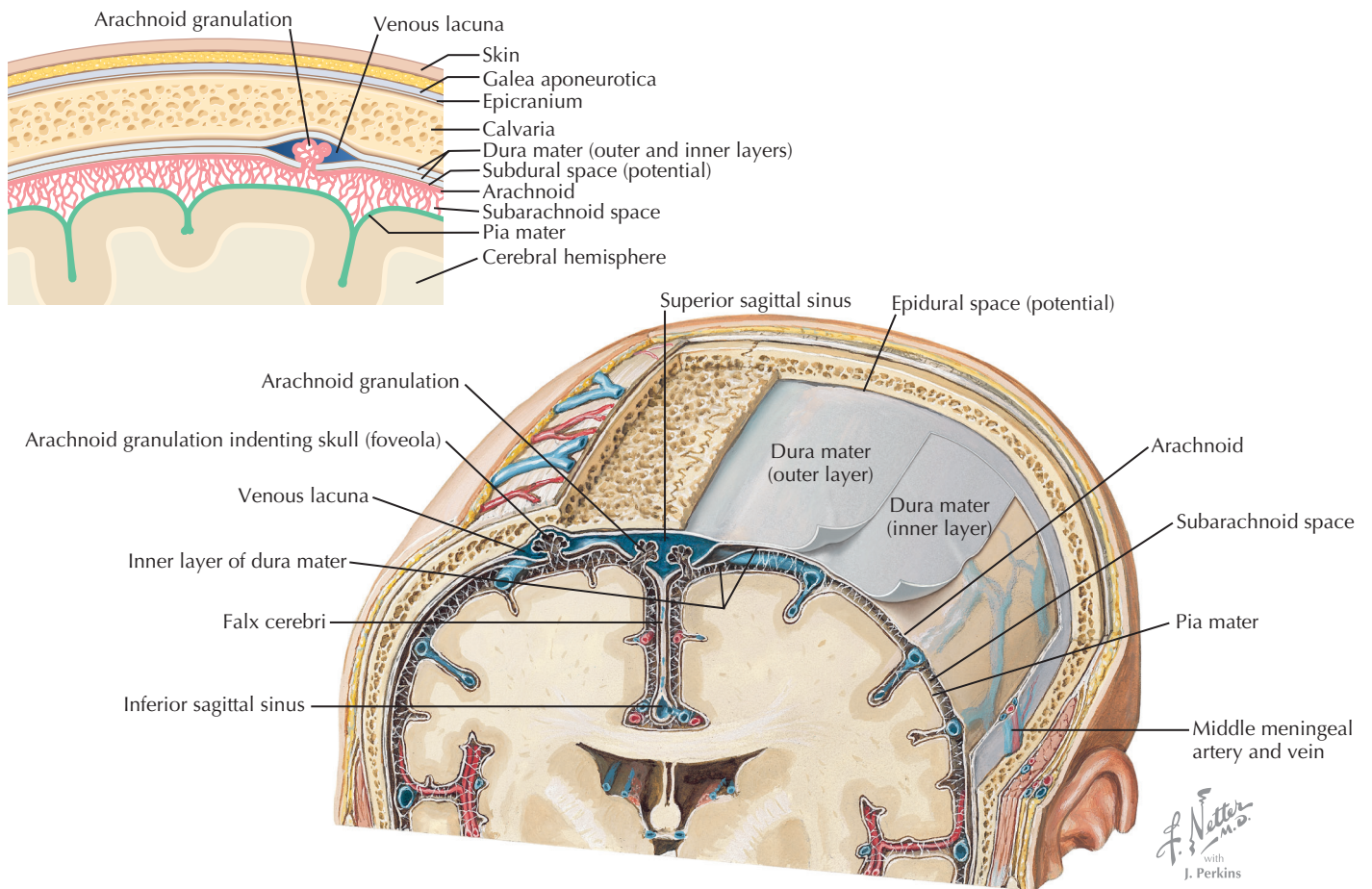




### 2.3 BONY FRAMEWORK OF THE HEAD AND NECK

The skull provides bony protection for the brain. The spine, consisting of vertebrae and their intervertebral disks, provides

bony protection for the spinal cord. The spine and skull articulate at the foramen magnum, where the C1 vertebral body (the atlas) abuts the occipital bone.



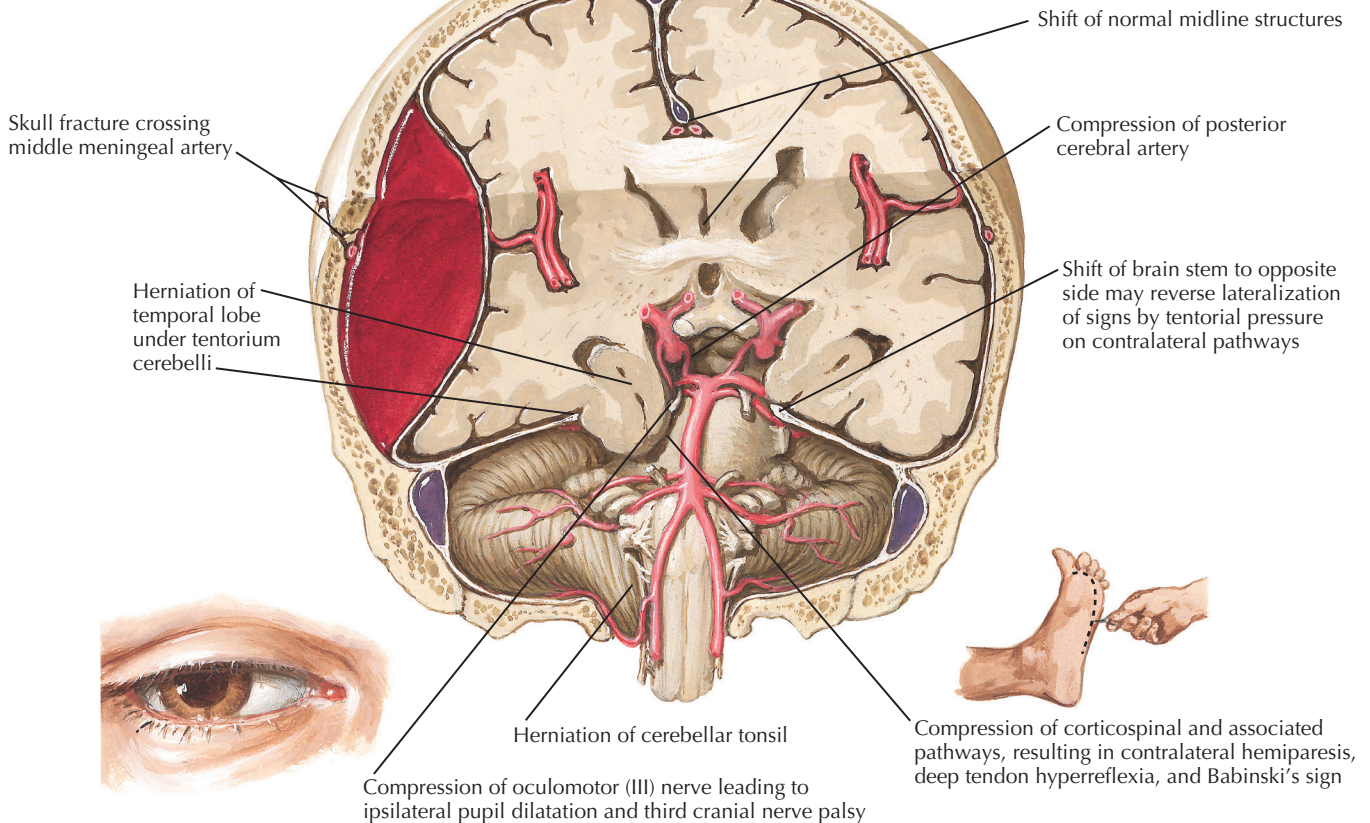
## 2.4 SCHEMATIC OF THE MENINGES AND THEIR RELATIONSHIPS TO THE BRAIN AND SKULL

The meninges provide protection and support for neural tissue in the central nervous system. The innermost membrane, the pia mater, adheres to every contour of neural tissue, including sulci, folia, and other infoldings. It adheres tightly to glial endfoot processes of astrocytes; this association is called the pial-glial membrane. The arachnoid mater, a fine, lacy membrane external to the pia, extends across the neural sulci and foldings. The space between these two membranes is the subarachnoid space, a space into which the cerebrospinal fluid flows, providing buoyancy and protection for the brain. Arteries and veins run through the subarachnoid space to and from the central nervous system. The rupture of an arterial aneurysm in a cerebral artery results in a subarachnoid hemorrhage. The dura mater, usually adherent to the inner arachnoid, is a tough protective outer membrane. It splits into two layers in some locations to provide channels, the venous sinuses, for return flow of the venous blood. The arachnoid granulations, one-way valves, extend from the subarachnoid space into the venous sinuses, especially the superior sagittal sinus, allowing cerebrospinal fluid to drain into the venous

blood and return to the heart. Blockage of these arachnoid granulations (e.g., in acute purulent meningitis) can result in increased intracranial pressure. Cerebral arteries and veins traverse the subarachnoid space. The veins, called bridging veins, drain into the dural sinuses. As they enter the sinus, these bridging veins are subject to tearing in cases of head trauma. If there is atrophy in the brain, as occurs with age, these veins may tear with relatively minor head trauma; in younger adults, more severe head trauma is needed to tear these bridging veins. Such tearing permits venous blood to accumulate in the subdural space as it dissects the inner dura from the arachnoid. This process may be gradual (chronic subdural hematoma) in older individuals or may be abrupt (acute subdural hematoma) with severe head trauma. A subdural hematoma, especially when it occurs acutely, may be life-threatening as the result of increased intracranial pressure caused by accompanying edema and by the accumulation of the blood in the hematoma itself. The dura is closely adherent to the inner table of the skull. A skull fracture may tear a branch of the middle meningeal artery, permitting arterial blood to dissect the dura from the skull, resulting in an epidural hematoma.

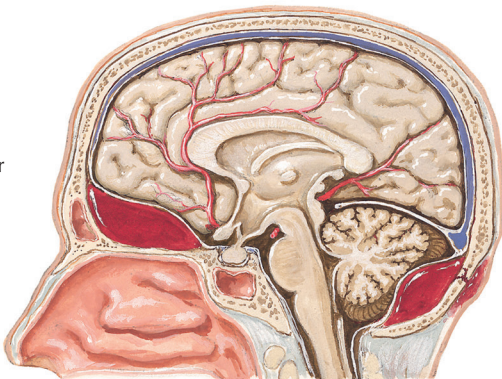


### Temporal Fossa Hematoma



### Subfrontal Hematoma

Frontal trauma: headache, poor cerebriation, intermittent disorientation, anisocoria



### Posterior Fossa Hematoma

Occipital trauma and/or fracture: headache, meningismus, cerebellar and cranial nerve signs, Cushing's triad



### Acute Subdural Hematoma

Section showing acute subdural hematoma on right side and subdural hematoma associated with temporal lobe intracerebral hematoma ("burst" temporal lobe) on left

## 2.5 HEMATOMAS

Epidural hematomas occur with trauma or skull fractures that tear meningeal arteries (especially middle meningeal artery branches). Blood from the tear dissects the outer layer of the dura from the skull, forming a space-occupying mass in what was normally only a potential space. The hematoma may compress adjacent brain tissue, producing localized signs, and may also cause herniation of distant brain regions across the free edge of the tentorium cerebelli (a transtentorial herniation) or across the falx cerebri (a subfalcine herniation). Such herniation may produce changes in consciousness, breathing, and blood pressure, and altered motor, pupillary, and other

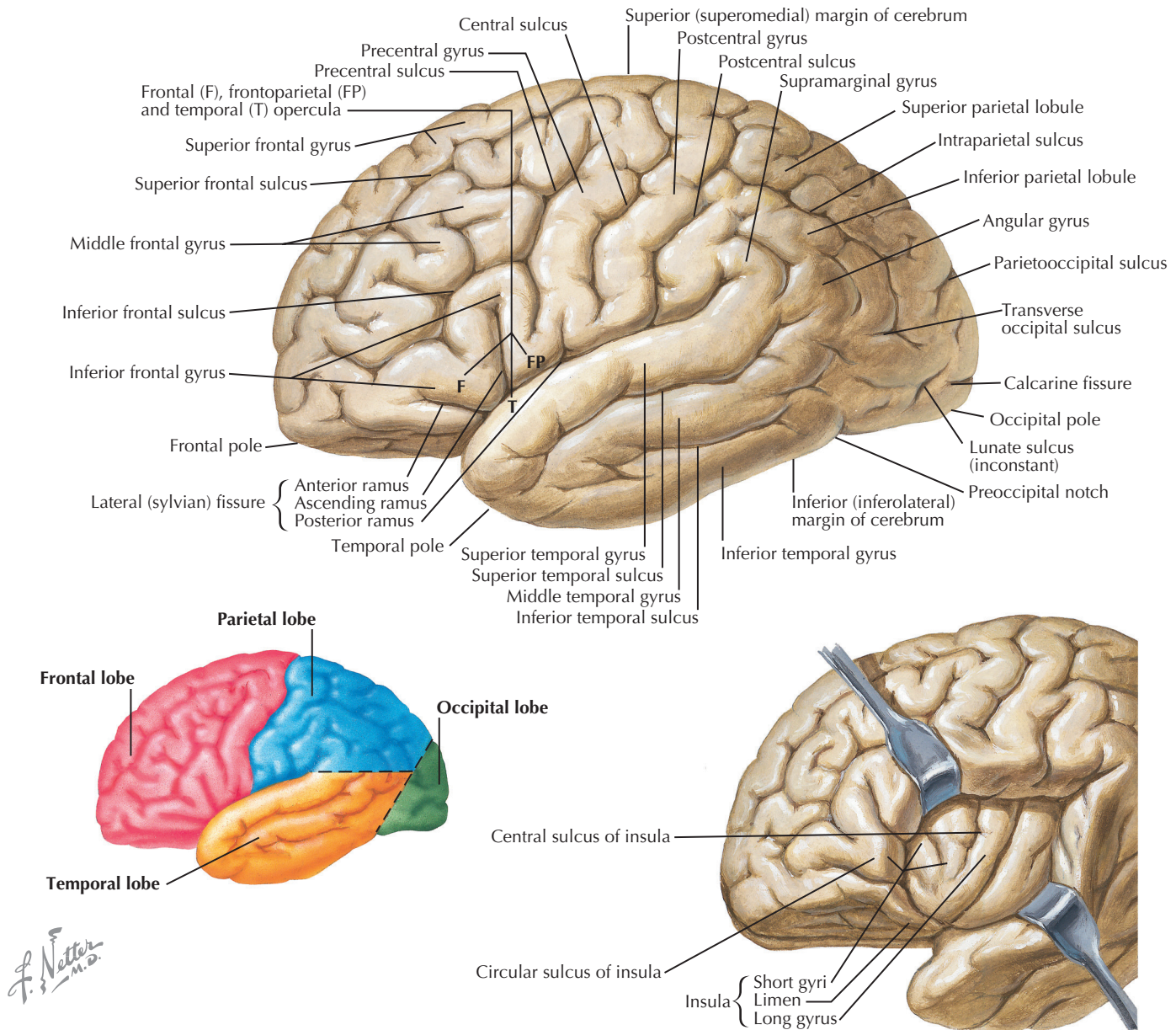
neurological signs. It may be fatal. Severe head trauma in an adult may tear bridging veins that lead from the brain through the subarachnoid space and into the dural sinuses, especially the superior sagittal sinus. The subsequent venous bleeding dissects the arachnoid membrane from the inner layer of the dura, and the blood accumulates as a subdural hematoma. The subdural space is normally only a potential space. Some of the proteins and other solutes in the hematoma attract edema, adding fluid accumulation to the hematoma and further exacerbating the space-occupying nature of the bleed. A subdural hematoma also may be associated with bleeding directly into the brain, an intracerebral hematoma.

# 3

## BRAIN

- 3.1 Surface Anatomy of the Forebrain: Lateral View
- 3.2 Lateral View of the Forebrain: Functional Regions
- 3.3 Lateral View of the Forebrain: Brodmann's Areas
- 3.4 Anatomy of the Medial (Midsagittal) Surface of the Brain in Situ
- 3.5 Anatomy of the Medial (Midsagittal) Surface of the Brain, with Brain Stem Removed
- 3.6 Medial Surface of the Brain
- 3.7 Anatomy of the Basal Surface of the Brain, with the Brain Stem and Cerebellum Removed
- 3.8 Basal Surface of the Brain: Functional Areas and Brodmann's Areas
- 3.9 Brain Imaging: Computed Tomography Scans, Coronal and Sagittal
- 3.10 Brain Imaging: Magnetic Resonance Imaging, Axial and Sagittal T1-Weighted Images
- 3.11 Brain Imaging: Magnetic Resonance Imaging, Axial and Sagittal T2-Weighted Images
- 3.12 Positron Emission Tomography Scanning
- 3.13 Horizontal Brain Sections Showing the Basal Ganglia
- 3.14 Major Limbic Forebrain Structures
- 3.15 Corpus Callosum
- 3.16 Color Imaging of the Corpus Callosum by Diffusion Tensor Imaging
- 3.17 Hippocampal Formation and Fornix
- 3.18 Thalamic Anatomy
- 3.19 Thalamic Nuclei



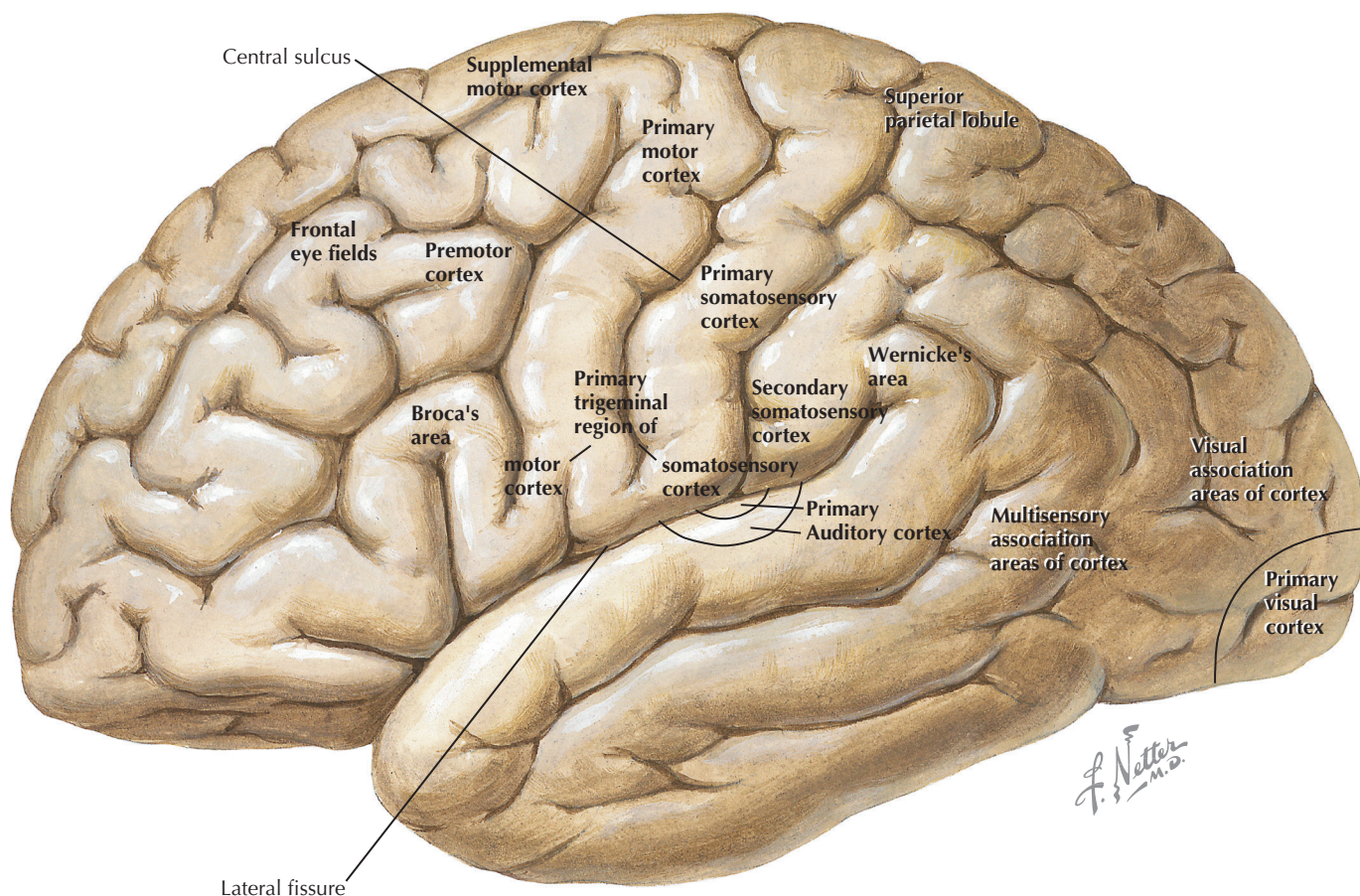


### 3.1 SURFACE ANATOMY OF THE FOREBRAIN: LATERAL VIEW

The convolutions of the cerebral cortex permit a large expanse of cortex to be compactly folded into a small volume, an adaptation particularly prominent in primates. Major dependable landmarks separate the forebrain into lobes; the lateral (sylvian) fissure separates the temporal lobe below from the parietal and frontal lobes above, and the central sulcus separates the parietal and frontal lobes from each other. Several of the named gyri are associated with specific functional activities, such as the precentral gyrus (motor cortex) and the postcentral gyrus (primary sensory cortex). Some gyri, such as the superior, middle, and inferior frontal and temporal gyri, serve as anatomical landmarks of the cerebral cortex. The insula, the fifth lobe of the cerebral cortex, is deep to the outer cortex and can be seen by opening the lateral fissure.

#### CLINICAL POINT

Some functional characteristics of the cerebral cortex, such as long-term memory and some cognitive capabilities, cannot be localized easily to a particular gyrus or region of cortex. However, other functional capabilities are regionally localized. For example, the inferior frontal gyrus on the left contains the neuronal machinery for expressive language capabilities; the occipital pole, particularly along the upper and lower banks of the calcarine fissure, are specialized for visual processing from the retino-geniculo-calcarine system. Some very discrete lesions in further processing sites such as vision-related regions of the temporal lobe can result in specific deficits, such as agnosia for the recognition of faces or the inability to distinguish animate objects. This knowledge provides some clues about how feature extraction in sensory systems might be achieved in neuronal networks.



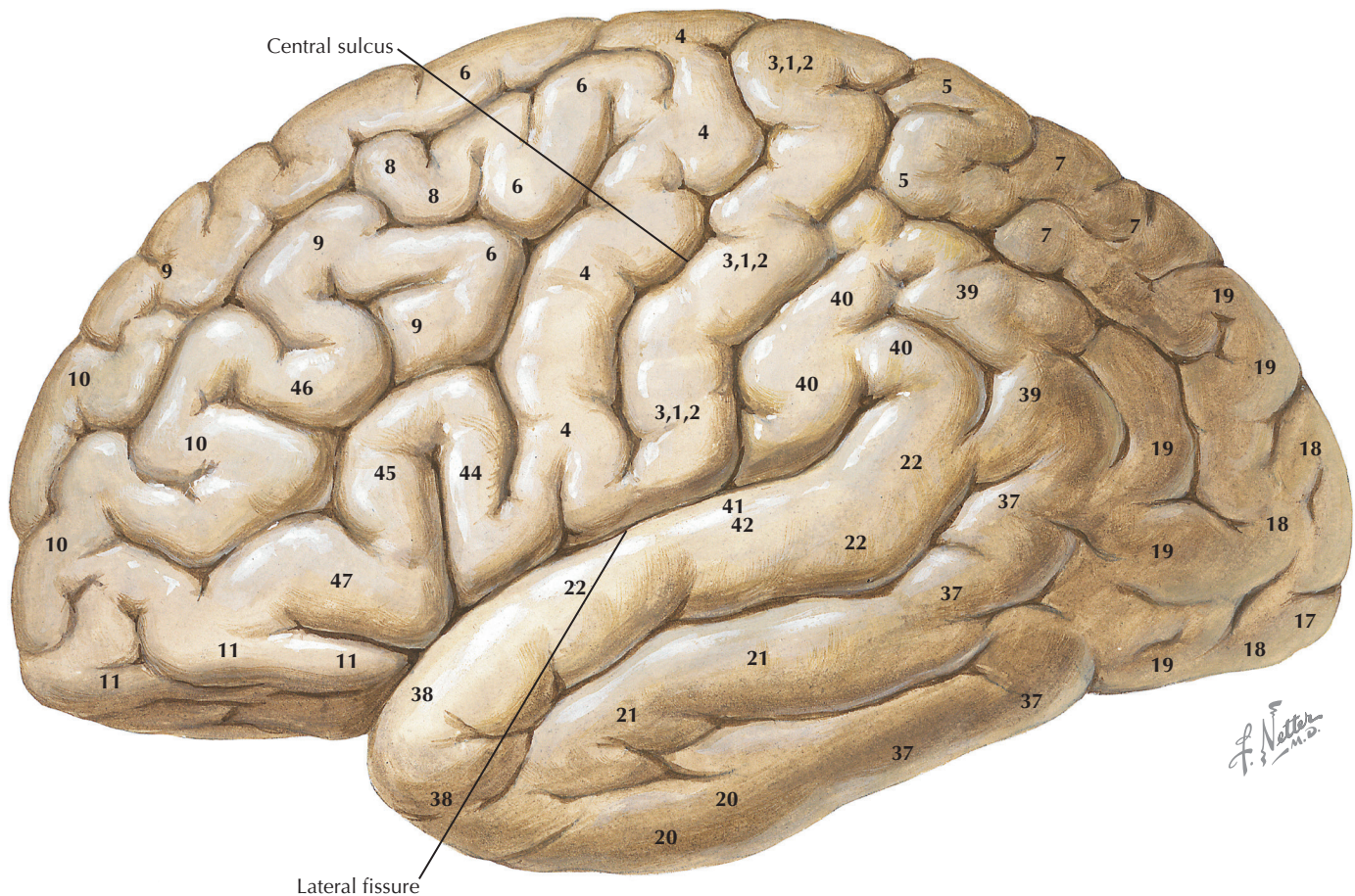
### 3.2 LATERAL VIEW OF THE FOREBRAIN: FUNCTIONAL REGIONS

Some circumscribed regions of the cerebral hemisphere are associated with specific functional activities, including the motor cortex, the supplemental and premotor cortices, the frontal eye fields, the primary sensory cortex, and other association regions of the sensory cortex. Part of the auditory cortex is visible at the inferior edge of the lateral fissure (the transverse temporal gyrus of Heschl). Part of the visual cortex is visible at the occipital pole. Language areas of the left hemisphere include Broca's area (expressive language) and Wernicke's area (receptive language). Damage to these cortical regions results in loss of specific functional capabilities. There is some overlap between functional areas and named gyri (e.g., the motor cortex and the precentral gyrus), but there is no absolute concordance.

#### CLINICAL POINT

Some specific regions (gyri) of the cerebral cortex, such as the precentral gyrus (primary motor cortex) and the postcentral gyrus (primary somatosensory cortex), demonstrate topographic organization. Thus, information from the contralateral hand and arm are localized laterally, the body is represented more medially, and the lower extremity is represented along the midline and over the edge into the paracentral lobule. The face and head are represented in far lateral regions of these gyri, just above the lateral fissure. This has important functional implications; damage to selected regions such as the midline territory, which is supplied with blood from the anterior cerebral artery, results in somatosensory loss and paresis in the contralateral lower extremity, while sparing the upper extremity.

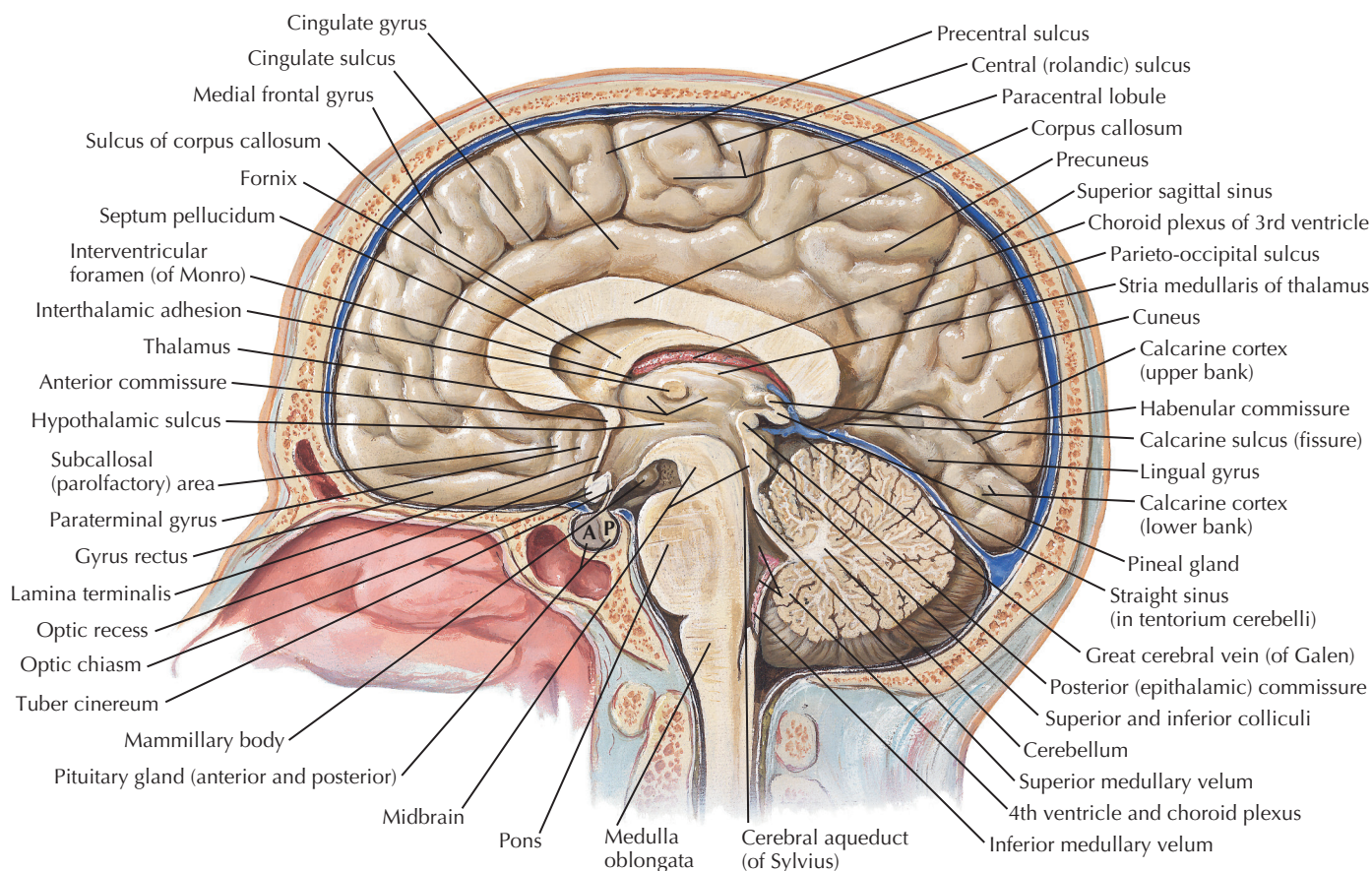




### 3.3 LATERAL VIEW OF THE FOREBRAIN: BRODMANN'S AREAS

Brodmann's areas of the cerebral cortex have unique architectural characteristics in terms of the thickness and layering of the cerebral cortex; this knowledge is based on histological observations originally made by Korbinian Brodmann in

1909. His numbering of cortical areas is still used as a shorthand for describing the functional regions of the cortex, particularly those related to sensory functions. Some overlap exists among functional areas. For example, the motor cortex is area 4; the primary sensory cortex includes areas 3, 1, and 2; and the primary visual cortex is area 17.



*F. Netter M.D.*

### 3.4 ANATOMY OF THE MEDIAL (MIDSAGITTAL) SURFACE OF THE BRAIN IN SITU

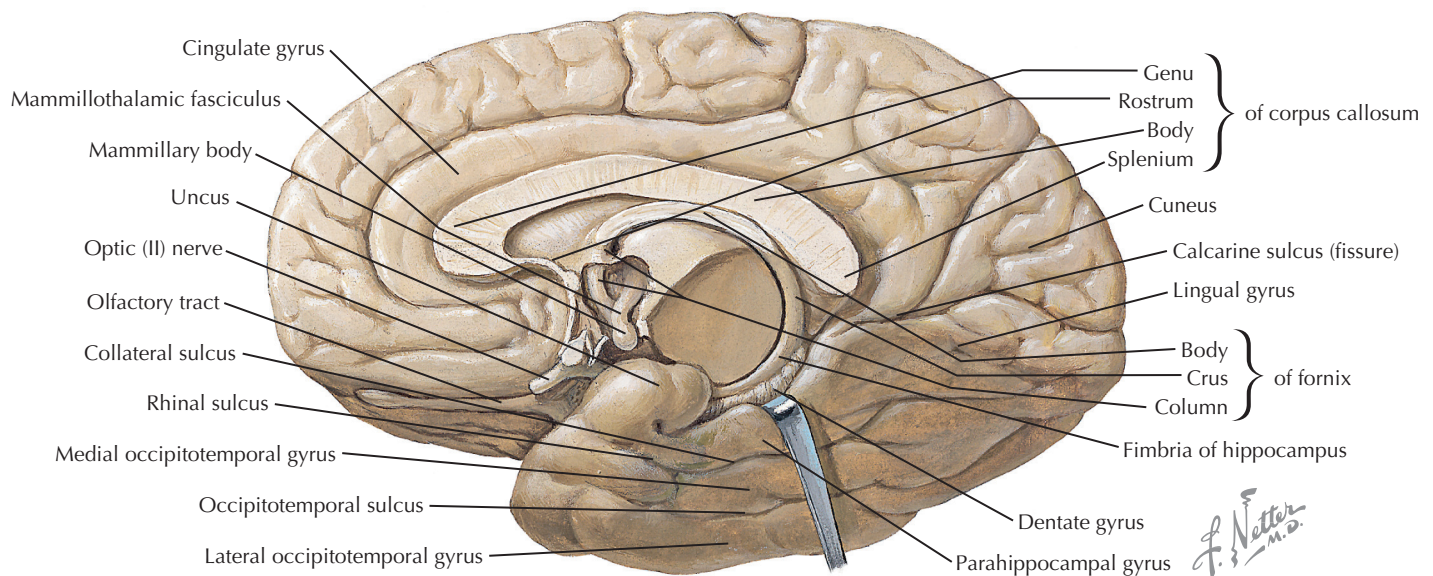
The entire extent of the neuraxis, from the spinomedullary junction through the brain stem, diencephalon, and telencephalon, is visible in a midsagittal section. The corpus callosum, a major commissural fiber bundle interconnecting the two hemispheres, is a landmark separating the cerebral cortex above from the thalamus, fornix, and subcortical forebrain below. The ventricular system, including the interventricular foramen (of Munro); the third ventricle (diencephalon); the cerebral aqueduct (midbrain); and the fourth ventricle (pons and medulla), is visible in a midsagittal view. This subarachnoid fluid system provides internal (the ventricular system) and external (cerebrospinal fluid in the subarachnoid space) protection to the brain and also may serve as a fluid transport system for important regulatory molecules. The thalamus serves as a gateway to the cortex. The hypothalamic proximity to the median eminence (tuber cinereum) and the pituitary

gland reflects the important role of the hypothalamus in regulating neuroendocrine function. A midsagittal view also reveals the midbrain colliculi, sometimes called the visual (superior) and auditory (inferior) tecta. See [Video 3-1](#).

#### CLINICAL POINT

The right and left hemispheres are interconnected by commissural fiber bundles. The largest is the corpus callosum, which interconnects all lobes with their counterparts. The anterior commissure interconnects regions of the temporal lobes. When these commissural fiber bundles are disconnected (split brain), the hemispheres do not know what their counterparts are doing, and inputs to one hemisphere cannot produce an appropriate response from the opposite hemisphere. With a split brain, only a more generalized recognition of mood states occurs between the two hemispheres, presumably communicated through interconnections between lower structures, such as the diencephalon and brain stem.

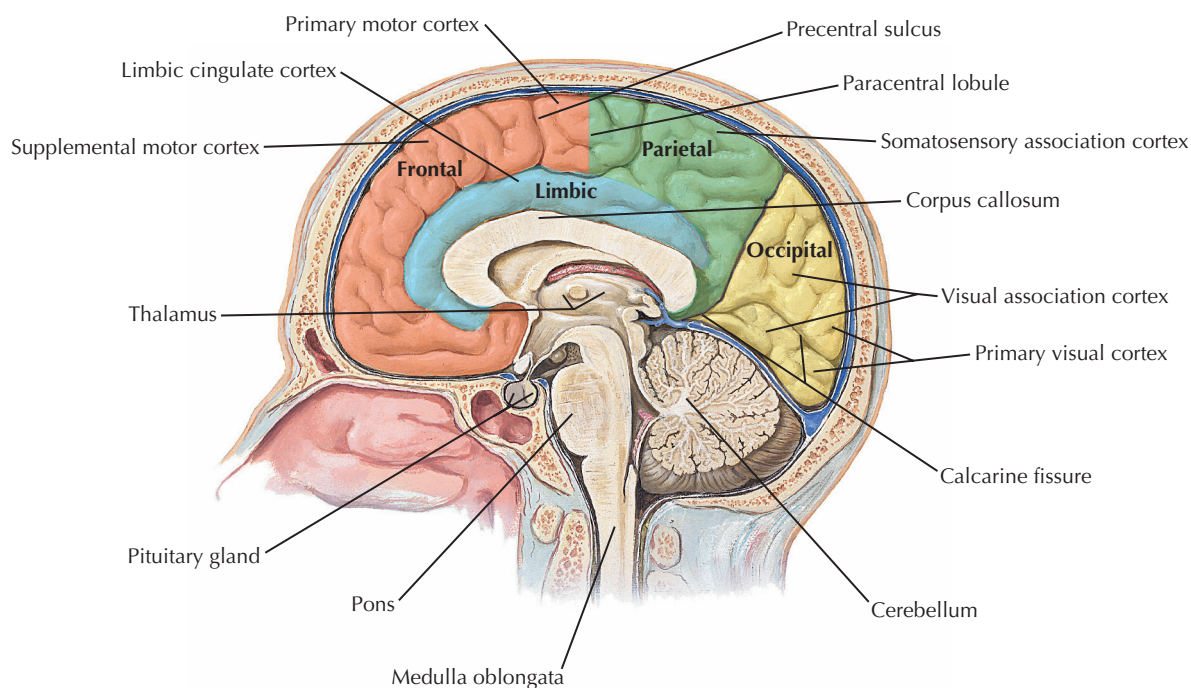




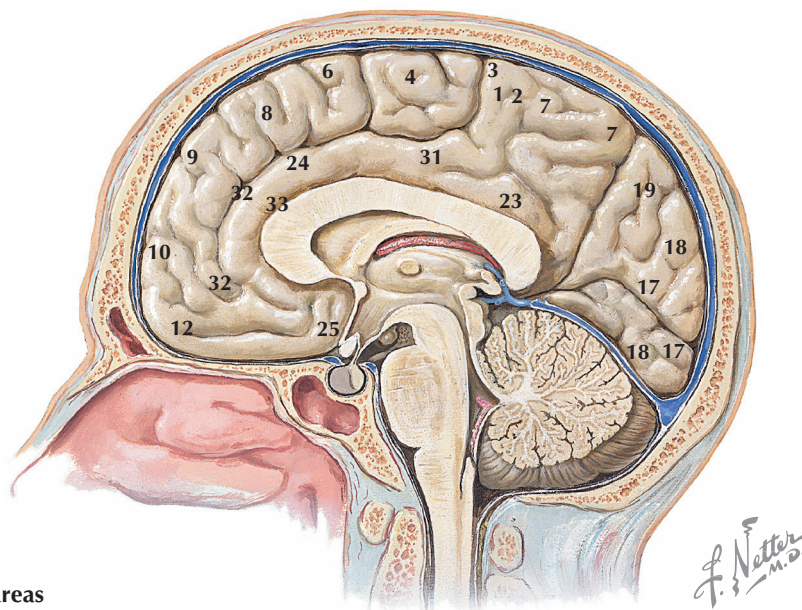
### 3.5 ANATOMY OF THE MEDIAL (MIDSAGITTAL) SURFACE OF THE BRAIN, WITH BRAIN STEM REMOVED

When the brain stem is removed, a midsagittal view reveals the C-shaped course of the fornix, extending from the hippocampal formation in the temporal lobe to the septum and

hypothalamus. Temporal lobe structures, such as the parahippocampal cortex, the dentate gyrus and fimbria of the hippocampus, and the uncus (olfactory cortex) also are visible. In the hypothalamus, the caudal mammillary bodies and the interconnecting pathway to the thalamus, the mammillothalamic tract, are revealed.



**A. Lobes and functional areas**



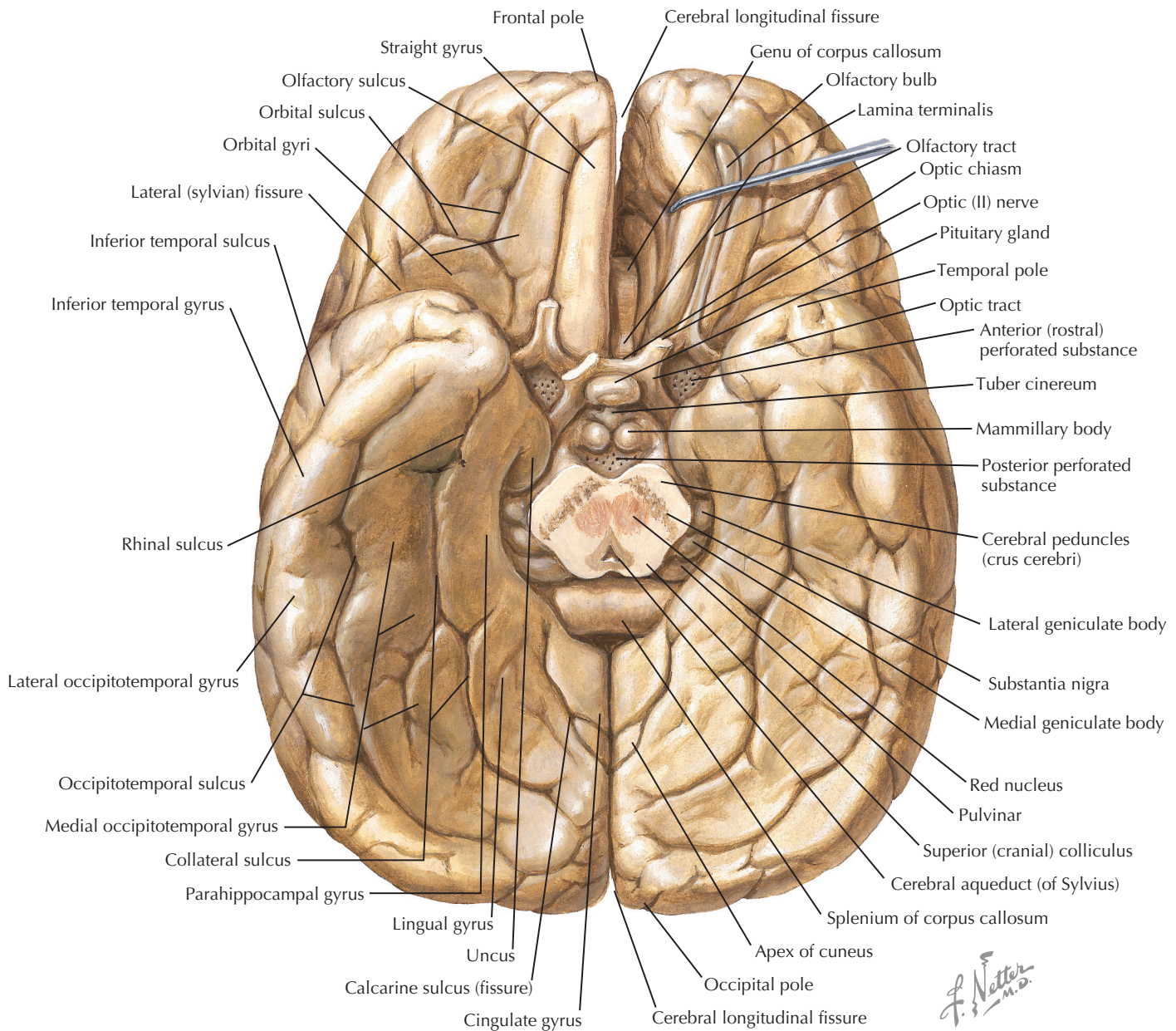
**B. Brodmann's areas**

### 3.6 MEDIAL SURFACE OF THE BRAIN

**A, Lobes and functional areas.** The cingulate cortex is labeled the limbic lobe, reflecting its association with other limbic forebrain structures and with hypothalamic control of the autonomic nervous system. Functional areas of the cortex, particularly those involved with vision, are best seen on a midsagittal view. The sensory and motor cortices associated with the lower extremities are located medially and are supplied with blood by the anterior cerebral artery. This region is

selectively vulnerable to specific vascular (anterior cerebral artery infarct) and mass (parasagittal meningioma) lesions that result in contralateral motor and sensory deficits of the lower extremity. **B, Brodmann's areas of the cerebral cortex** are labeled on this midsagittal view of the brain. The major regions are the primary (17) and associative (18, 19) visual cortices, and the continuation of areas 4 (motor) and areas 3, 1, and 2 (primary sensory) onto the paracentral lobule in the midline.





### 3.7 ANATOMY OF THE BASAL SURFACE OF THE BRAIN, WITH THE BRAIN STEM AND CEREBELLUM REMOVED

Removal of the brain stem and cerebellum by a cut through the midbrain exposes the underlying cerebral cortex, the base of the diencephalon, and the basal forebrain. Basal hypothalamic landmarks, from caudal to rostral, include the mammillary bodies, tuber cinereum, pituitary gland, and optic chiasm. The proximity of the pituitary to the optic chiasm is important because bitemporal hemianopsia can result from optic chiasm fiber damage, often an early sign of a pituitary tumor. The genu and splenium of the corpus callosum are revealed in this view. In the cross-section of the midbrain, the superior colliculus, cerebral aqueduct, periaqueductal gray, red nucleus, substantia nigra, and cerebral peduncles are shown.

#### CLINICAL POINT

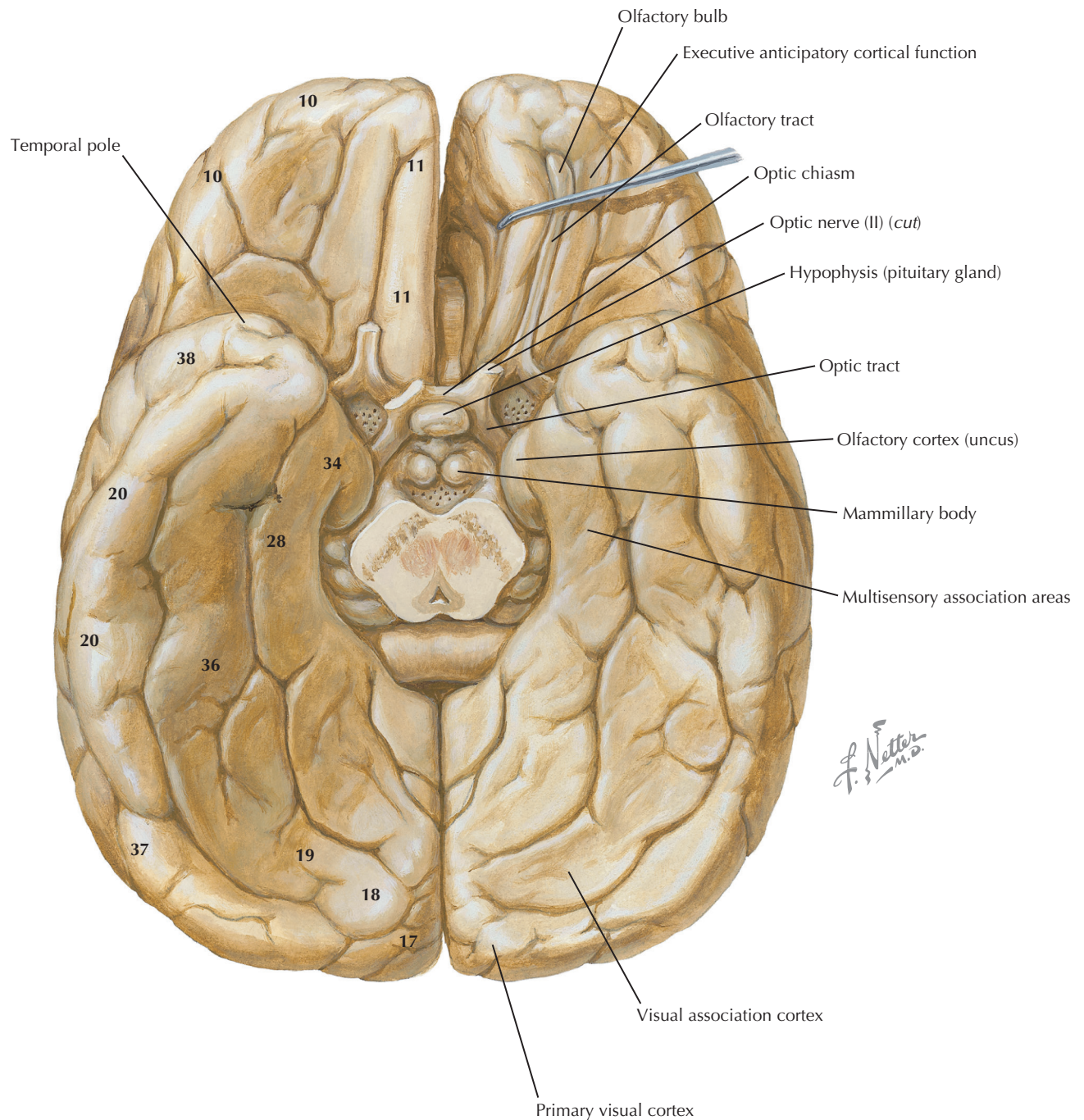
The olfactory bulb and tract send connections directly into limbic forebrain structures, such as the uncus (the primary olfactory cortex),

amygdala, and other limbic regions. This is the only sensory system with direct access to forebrain structures without prior screening through the diencephalon. This reflects the evolutionary importance of olfaction to functions vital for survival, such as detection of food, defense, and reproduction. Olfactory damage can alter emotional behavior. In addition, complex partial seizures involving the temporal lobe frequently are accompanied by an olfactory aura. Changes in olfactory function and gene expression may be among the earliest signs of Alzheimer's disease.

The optic nerve, chiasm, and tract can be seen extending toward the lateral geniculate body (nucleus), the pulvinar, and the superior colliculus. Optic nerve damage can result in ipsilateral blindness; optic chiasm damage can result in bitemporal visual field deficits; and optic tract damage can result in contralateral hemianopsia. Additional visual input from the optic tract enters the hypothalamus and ends in the suprachiasmatic nucleus. This visual input conveys information of total light flux and exposure, permitting visual influence over diurnal rhythms such as the cortisol rhythm. Disruption of this diurnal input can produce altered production of hormones such as melatonin, and metabolic consequences such as the propensity for abdominal obesity resulting from disruption of the diurnal cortisol rhythm.

## Brodmann's areas

## Structures



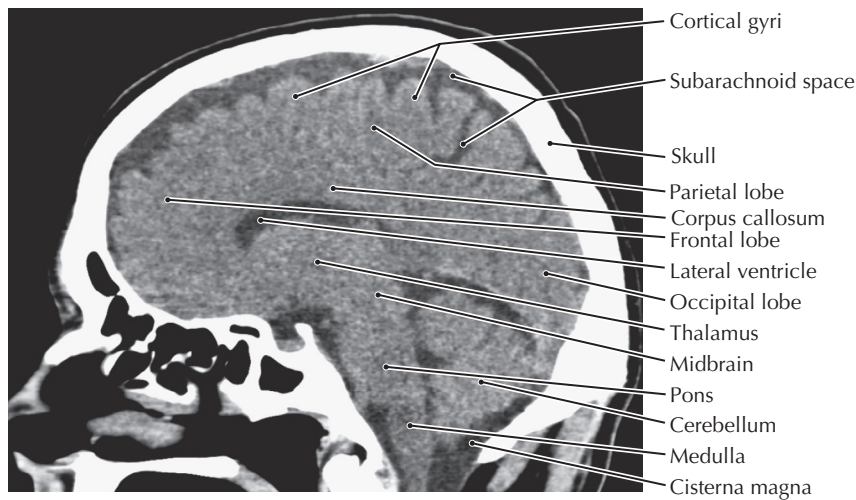
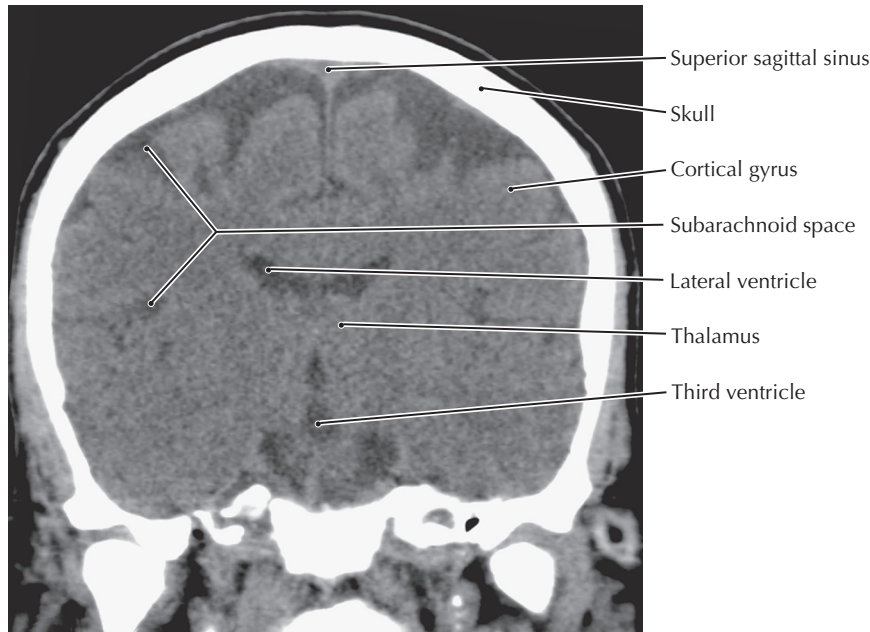
### 3.8 BASAL SURFACE OF THE BRAIN: FUNCTIONAL AREAS AND BRODMANN'S AREAS

This view provides information about the medial temporal lobe on the left side of the brain, especially cortical regions

associated with the hippocampal formation, the amygdaloid nuclei, and the olfactory system. On the right side of the brain, Brodmann's areas are noted.



A. Coronal view



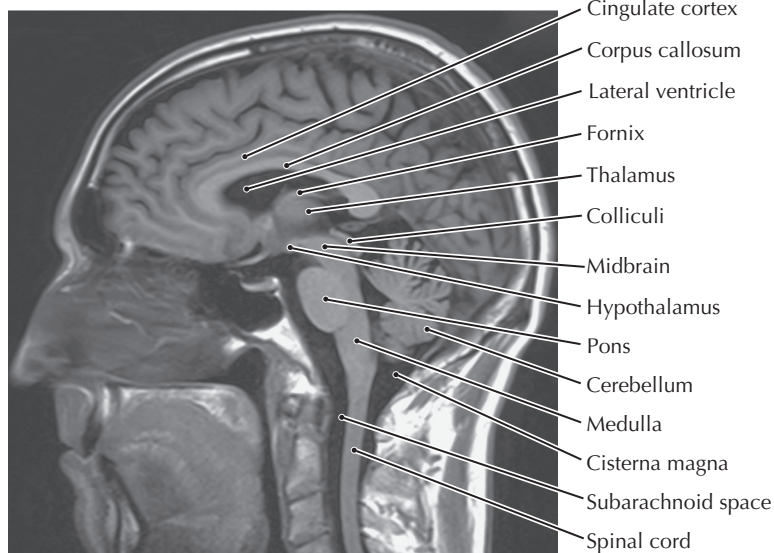
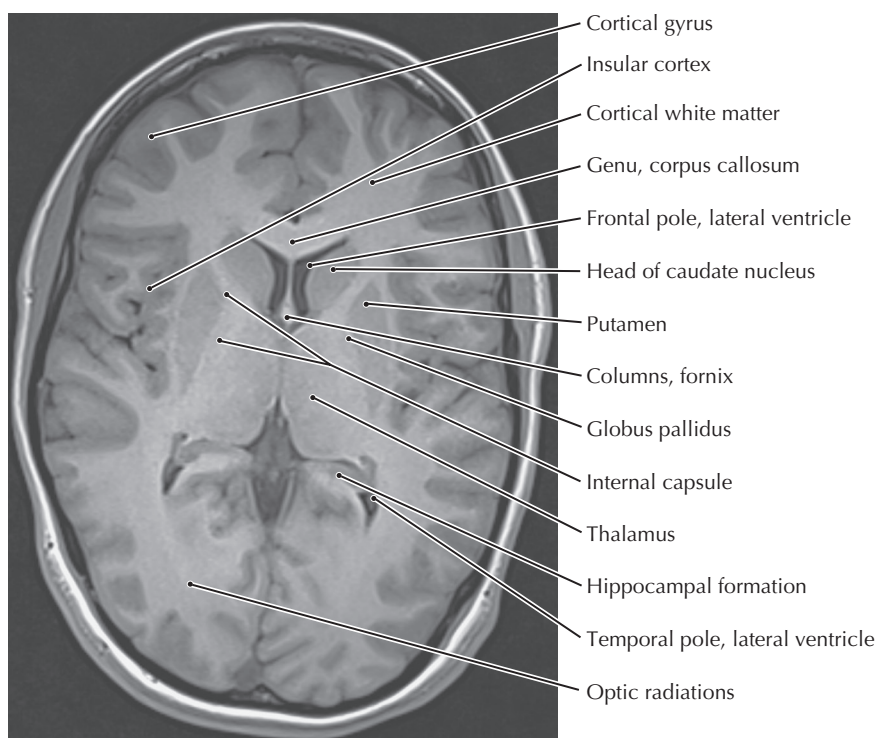
B. Sagittal view

### 3.9 BRAIN IMAGING: COMPUTED TOMOGRAPHY SCANS, CORONAL AND SAGITTAL

A and B, Computed tomography (CT) is an x-ray–based imaging approach that is used to view the brain, particularly when looking for differences in tissue density such as the presence of blood. The use of spiral (helical) scanners can quickly

provide access to views of slices through the brain at a desired thickness. CT delineates soft tissue, fluid, and bone and can be used with contrast to image blood vessels or to reveal the presence of a tumor caused by a disrupted blood-brain barrier, which allows leakage of the contrast agent into the surrounding extracellular space of the brain.

## A. Axial view



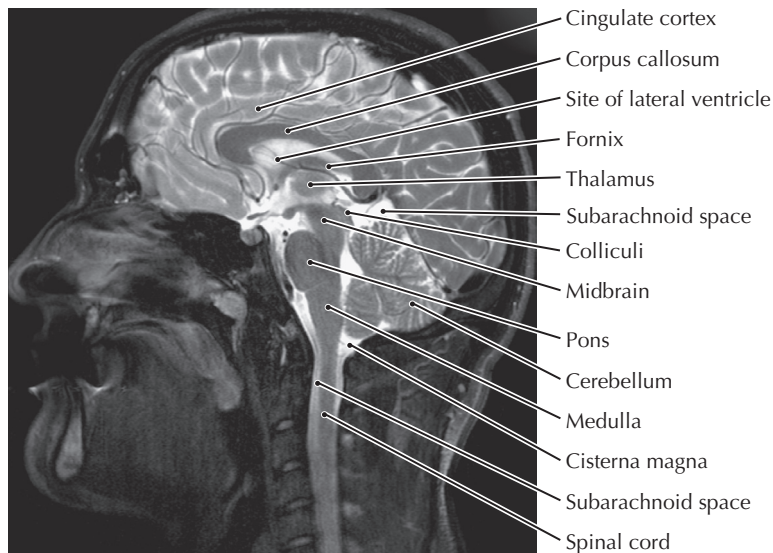
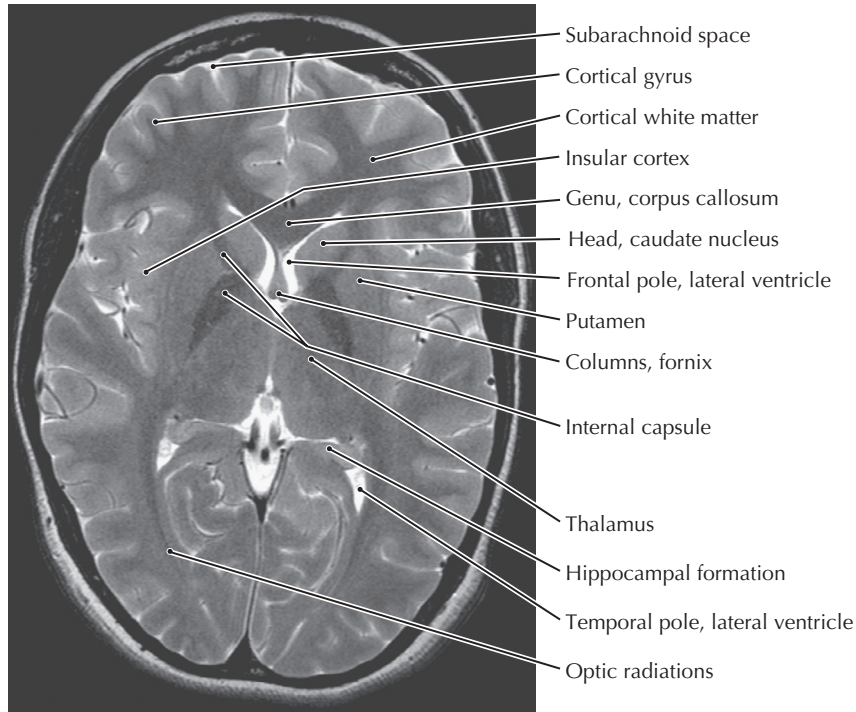
## B. Sagittal view

### 3.10 BRAIN IMAGING: MAGNETIC RESONANCE IMAGING, AXIAL AND SAGITTAL T1-WEIGHTED IMAGES

**A, axial view. B, sagittal view.** Magnetic resonance imaging (MRI) uses short bursts (radiofrequency pulses) of electromagnetic waves that are sent into the magnet and are absorbed by protons in the tissues of the patient in the scanner. The pulses cause alignment of the protons as the result of raised energy levels; that is followed by a relaxation phase in which the protons return to a lower energy level. During the relaxation process, a detector records the emitted energy, and a computer provides a uniform image of the scanned tissue. The intervals (milliseconds) between the pulses (repetition time, TR) and the intervals between the collection times of the

emitted energy (echo time, TE) provide various contrast information, which are indicated by contrast weighting. Short TR and TE intervals result in T1-weighted images, whereas longer TR and TE intervals result in T2-weighted images. The T1-weighted images are particularly useful for viewing normal brain structures and are particularly useful for viewing the brain stem and the cervical and thoracic spinal cord. The ventricular system and subarachnoid space in T1-weighted images appear dark. The T2-weighted images are particularly useful for revealing pathology, such as infarcts, tumors, edema, and demyelination. A contrast agent such as gadolinium can be used to delineate a tumor because of its ability to leak across the blood-brain barrier.

A. Axial view



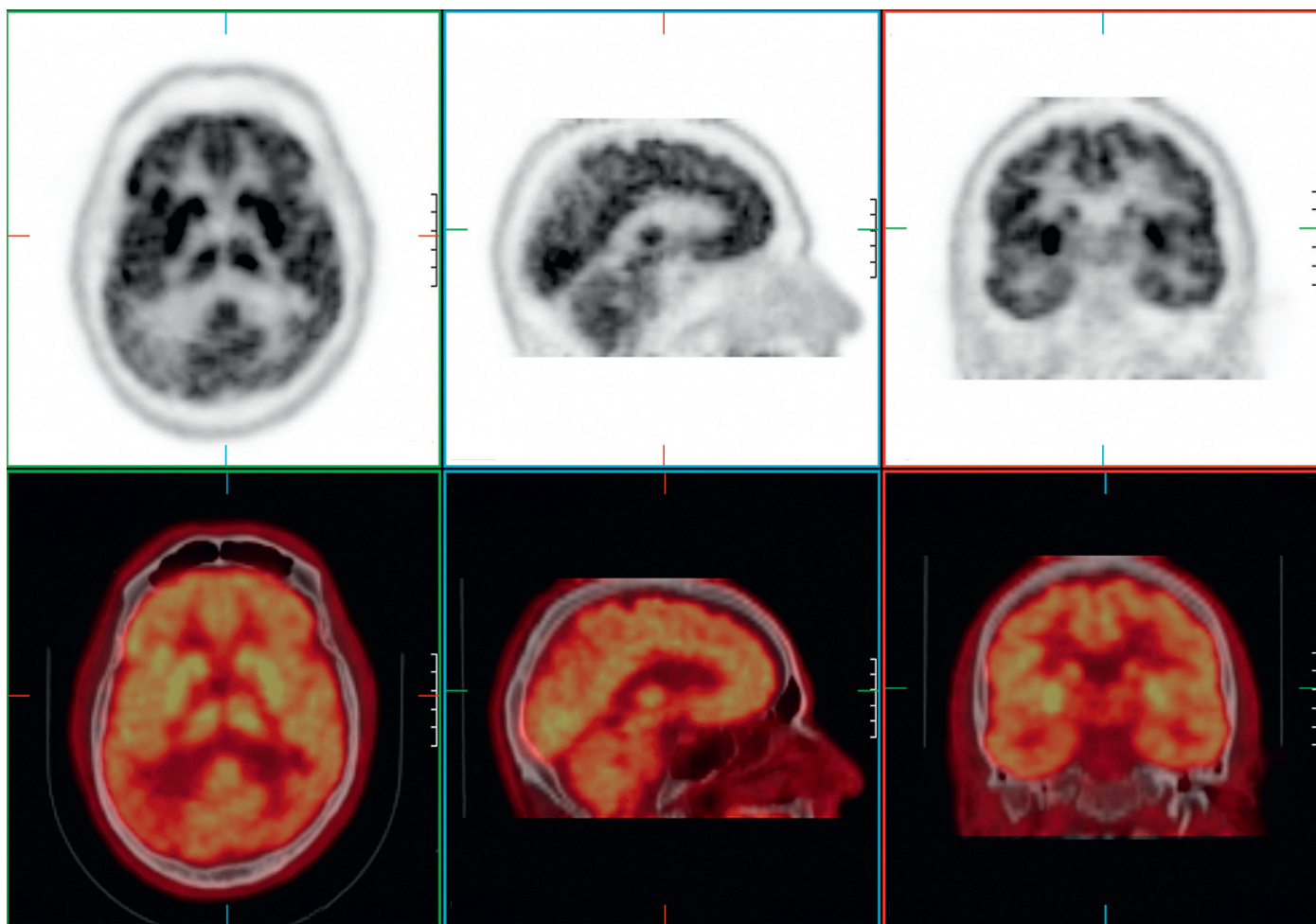
B. Sagittal view

### 3.11 BRAIN IMAGING: MAGNETIC RESONANCE IMAGING, AXIAL AND SAGITTAL T2-WEIGHTED IMAGES

A, axial view. B, sagittal view. T2-weighted images are particularly useful for imaging the ventricular system and the cisterns

of cerebrospinal fluid. The ventricular system and subarachnoid space in T2-weighted images appear white.



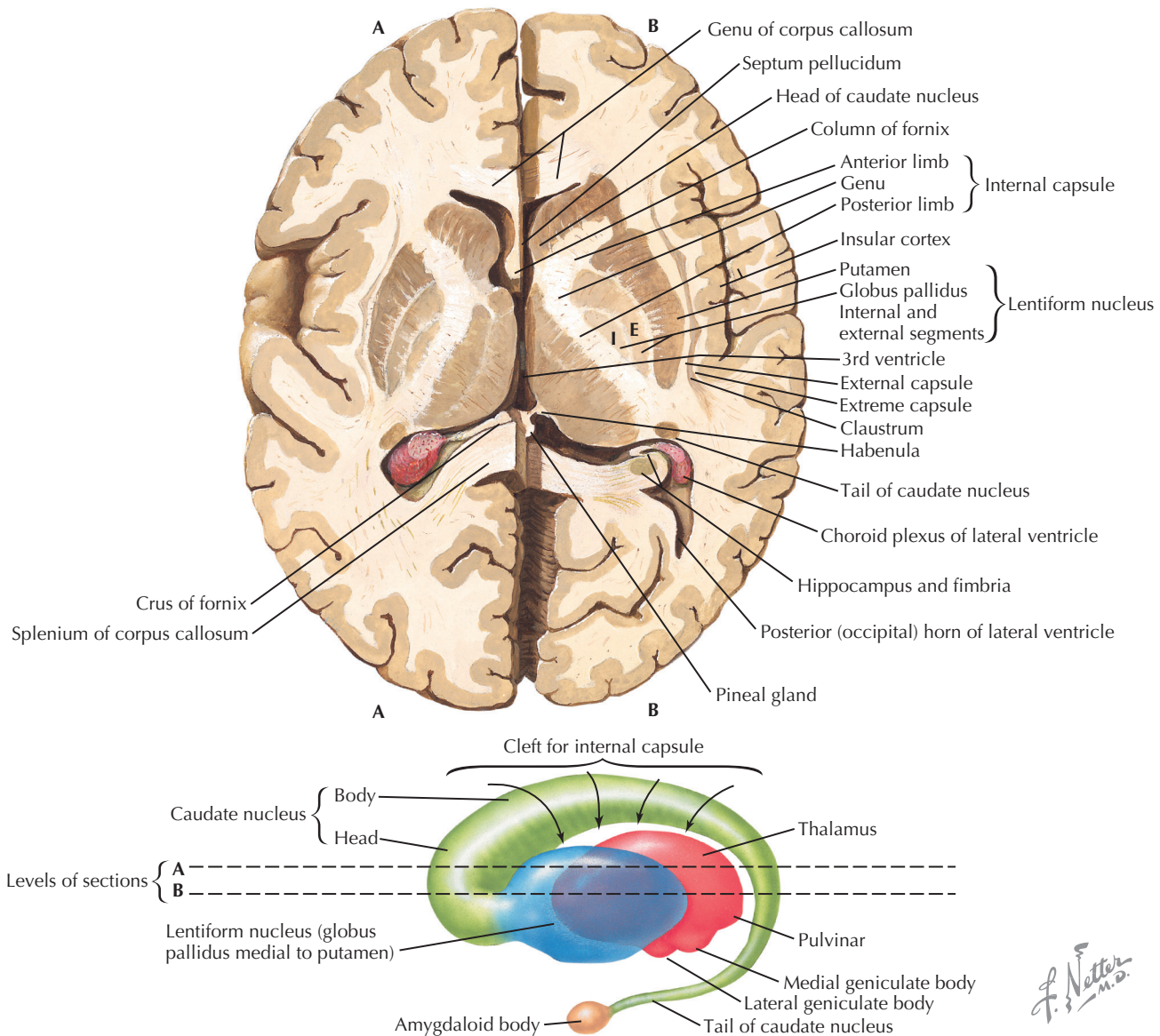


### 3.12 POSITRON EMISSION TOMOGRAPHY SCANNING

Positron emission tomography (PET) scanning is designed to assess the distribution of tracers labeled with positron-emitting nuclides, such as carbon-11 ( $^{11}\text{C}$ ), nitrogen-13 ( $^{13}\text{N}$ ), oxygen-15 ( $^{15}\text{O}$ ), and fluorine-18 ( $^{18}\text{F}$ ). Fluorodeoxyglucose (FDG), a glucose analogue labeled with  $^{18}\text{F}$ , can cross the blood-brain barrier. The metabolic products of FDG become immobile and trapped where the molecule is first used, thereby permitting FDG to be used to map glucose uptake in the brain.

This is a valuable tool for investigating subtle physiological processes related to neurological diseases. The distribution of FDG can be localized and reconstructed using standard tomographic techniques that show the tracer distribution throughout the body or brain. In this example of axial, sagittal, and coronal views, the transmission measurement and correction was performed immediately following PET acquisition using a 16-slice CT unit. The PET and CT images were automatically fused by anatomical coregistration software (shown as colored images).





Schematic illustration showing interrelationship of thalamus, lentiform nucleus, caudate nucleus, and amygdaloid body (viewed from side).

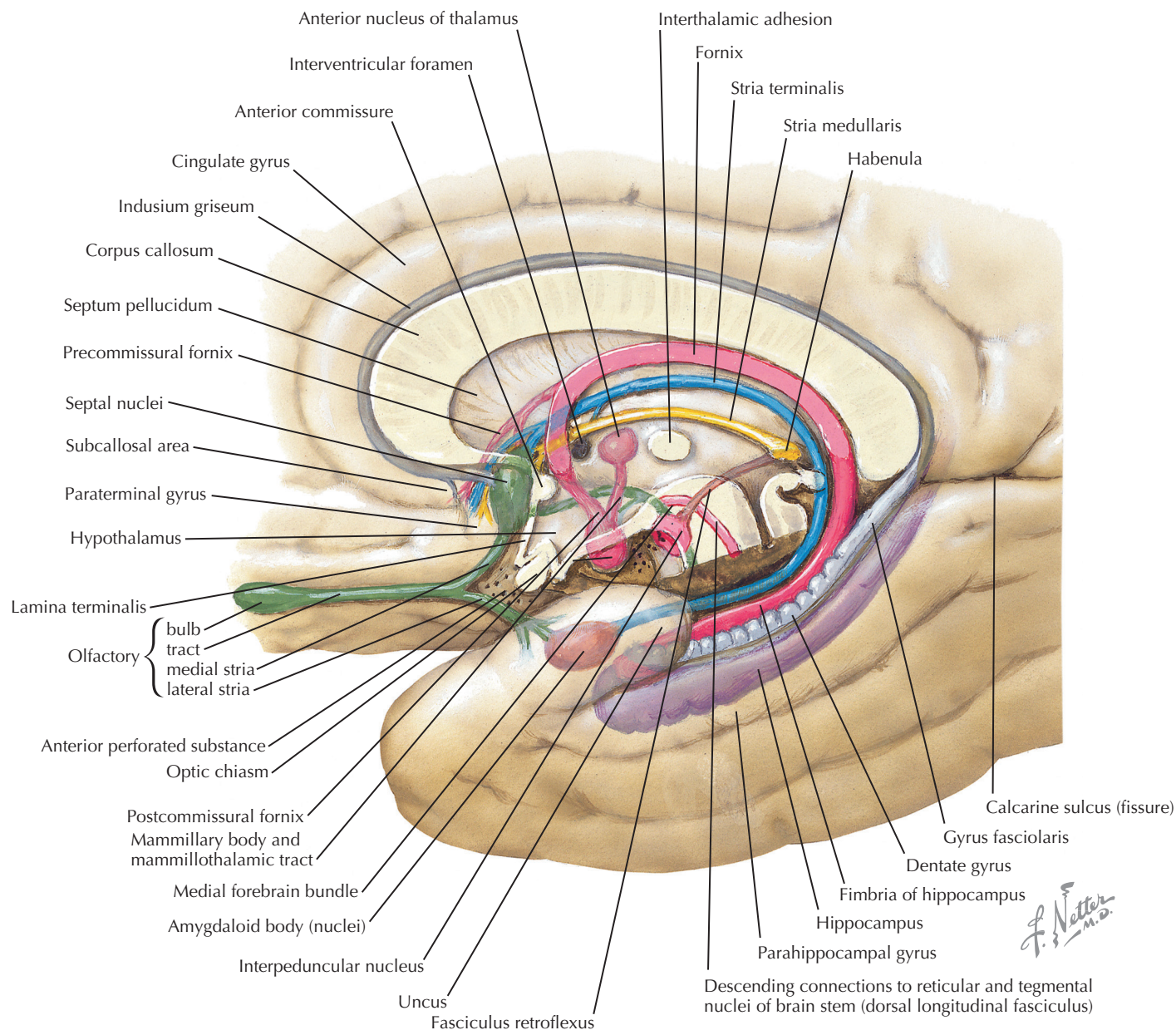
### 3.13 HORIZONTAL BRAIN SECTIONS SHOWING THE BASAL GANGLIA

Two levels of horizontal sections through the forebrain reveal the major anatomical features and the relationships among the basal ganglia, the internal capsule, and the thalamus (schematically shown in the lower illustration). The caudate nucleus is a C-shaped structure that sweeps from the frontal lobe into the temporal lobe; a horizontal section passes through this nucleus in two distinct places (head and tail). The anterior limb, genu, and posterior limb of the internal capsule contain major connections into and out of the cerebral cortex. The head and body of the caudate are medial to the anterior limb, whereas the thalamus is medial to the posterior limb. These relationships are important for understanding imaging studies and for understanding the involvement of specific functional systems in vascular lesions or strokes. The internal and external segments of the globus pallidus are located medial to the putamen. The external capsule, claustrum, extreme capsule,

and insular cortex, from medial to lateral, are located lateral to the putamen. The fornix, also a C-shaped bundle, is sectioned in two sites, the crus and the column.

#### CLINICAL POINT

The basal ganglia (caudate nucleus, putamen, and globus pallidus) form characteristic anatomical relationships with the internal capsule. The head and body of the caudate nucleus are found medial to the anterior limb; the thalamus is found medial to the posterior limb; and the globus pallidus and putamen are found lateral to the anterior and posterior limbs. Basal ganglia disorders are characterized by movement disorders, although emotional and cognitive symptoms also are seen. Some movement disorders involve actual degeneration of basal ganglia and related structures; these disorders include Huntington's chorea and degeneration of the head of the caudate nucleus as well as Parkinson's disease and degeneration of the dopaminergic pars compacta of substantia nigra. Other movement disorders involve altered inhibitory and excitatory activity of specific portions of basal ganglia circuitry; reordering this circuitry may require pharmacologic treatment, therapeutic ablation procedures, or deep brain stimulation.



### 3.14 MAJOR LIMBIC FOREBRAIN STRUCTURES

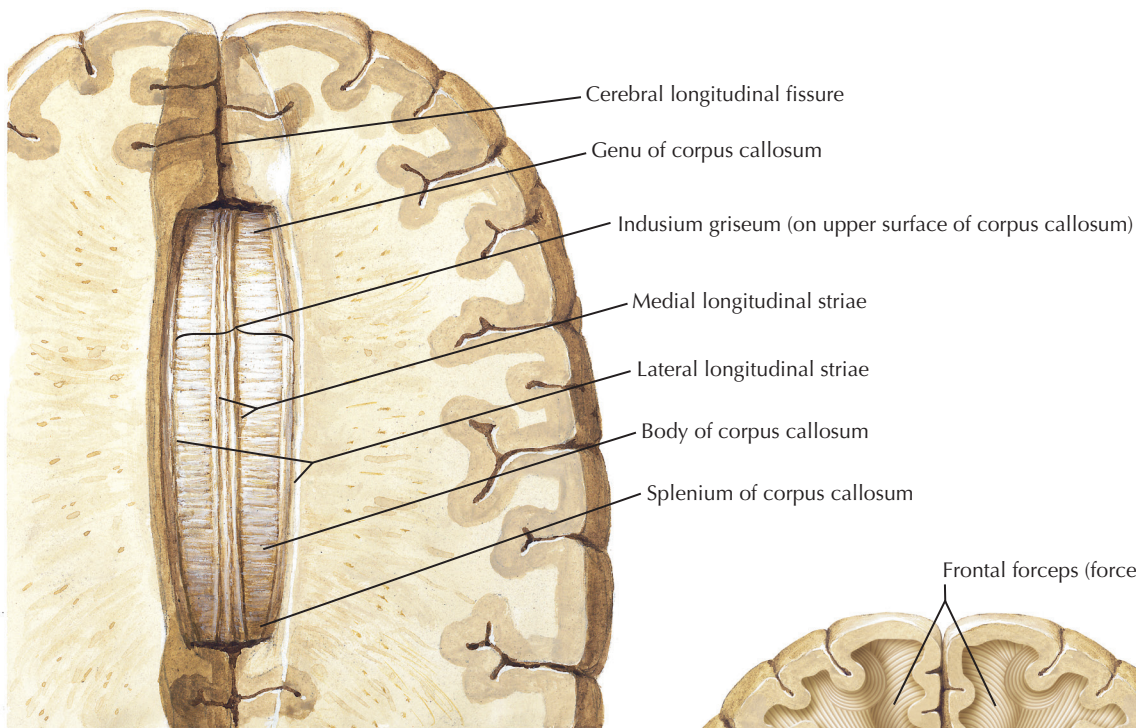
The term *limbic* is derived from *limbus*, meaning ring. Many of these structures and their pathways in the limbic system form a ring around the diencephalon. They are involved in emotional behavior and individualized interpretations of external and internal stimuli. The hippocampal formation and its major pathway, the fornix, curve into the anterior pole of the diencephalon, forming precommissural (to the septum) and postcommissural (to the hypothalamus) connections in relation to the anterior commissure. The amygdaloid nuclei give rise to several pathways; one, the stria terminalis, extends in a C-shaped course around the diencephalon into the hypothalamus and basal forebrain. The olfactory tract communicates directly with several limbic forebrain areas; it is the only sensory system to entirely bypass the thalamus and terminate directly in cortical and subcortical zones of the telencephalon. Connections from the septal nuclei to the habenula (stria medullaris thalami) connect the limbic forebrain to the brain stem. The amygdaloid nuclei and hippocampus (shaded) are deep to the cortex.

#### CLINICAL POINT

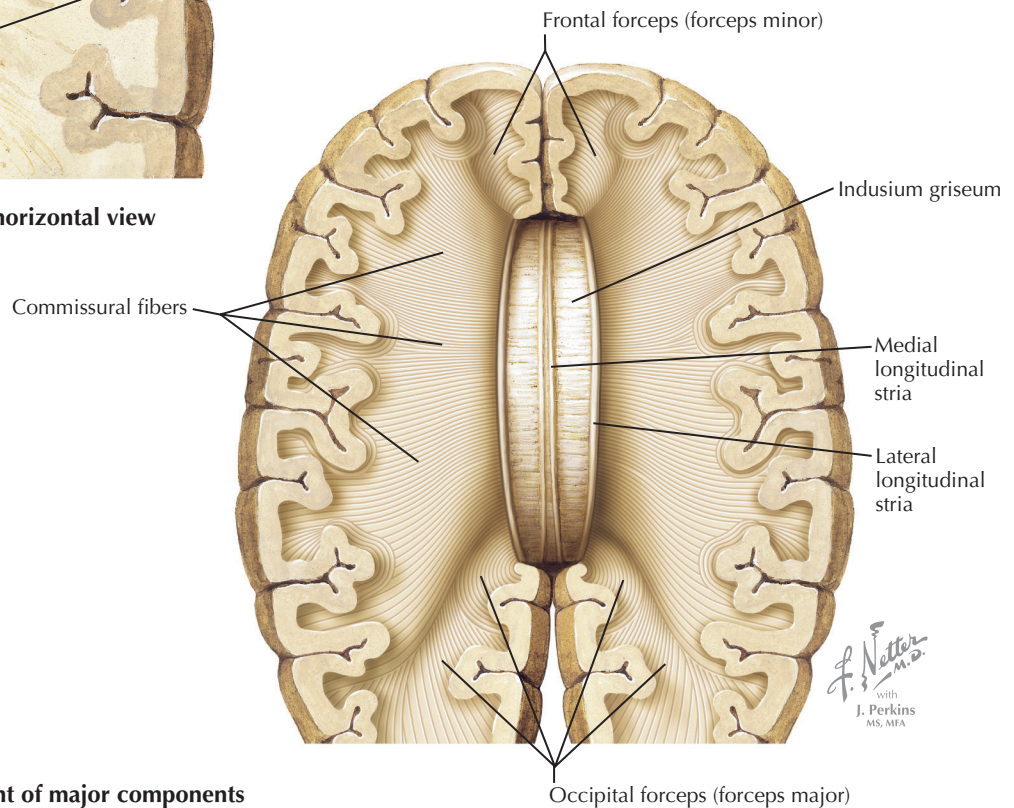
Many of the limbic forebrain structures are connected with the hypothalamus by C-shaped structures, such as the hippocampus and the fornix, and with the amygdala and the stria terminalis. The amygdala has additional direct connections into the hypothalamus via the ventral amygdalofugal pathway. The amygdaloid nuclei receive multi-modal sensory information from cortical regions and provide context for this input, particularly emotions related to fear responses. Bilateral amygdaloid damage results in the loss of the fear response and also in failure to recognize facial responses of fear in others.

The hippocampal formation processes abundant information from the temporal lobe, subiculum, and entorhinal cortex and sends connections through the fornix to the hypothalamus and septal nuclei, with subsequent connections through the thalamus to the cingulate cortex. These structures are part of the so-called Papez circuit. The hippocampal formation is particularly vulnerable to ischemia; damage bilaterally results in the inability to consolidate new information into long-term memory. A common pattern may be observed in older persons who forget who has talked with them minutes before or forget what they had for breakfast (or even whether they had breakfast) but can recall details from the past that have some degree of accuracy.





**A. Anatomy of the corpus callosum: horizontal view**



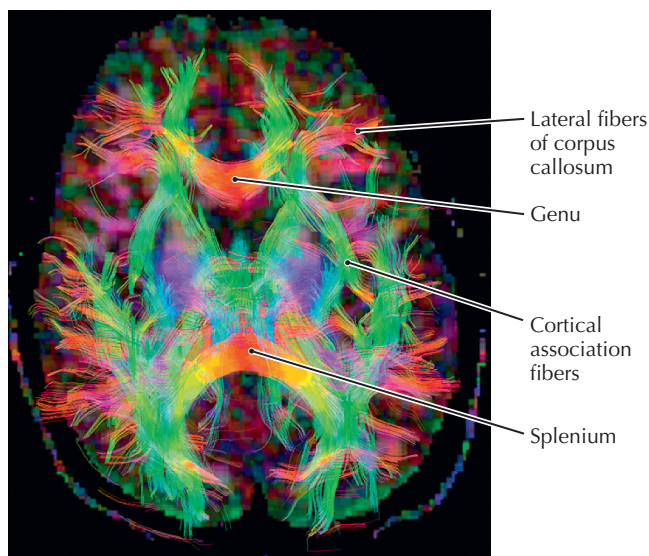
**B. Schematic view of the lateral extent of major components**

### 3.15 CORPUS CALLOSUM

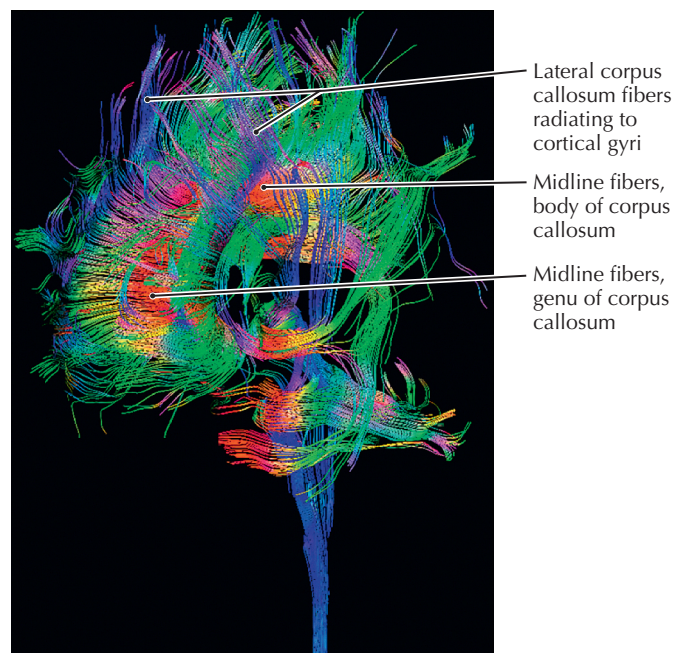
**A**, Anatomy of the corpus callosum, horizontal view. The corpus callosum, the major fiber commissure between the hemispheres, is a conspicuous landmark in imaging studies. It is viewed from above after dissection of tissue just dorsal to its upper surface. Horizontal cuts taken deeper (more ventrally) section the genu anteriorly and the splenium posteriorly (see [Fig. 3.13](#)). **B**, Schematic view of the lateral extent of

major components. Many of the commissural fibers of the corpus callosum, particularly the forceps of commissural fibers that interconnect frontal areas with each other and occipital areas with each other, extend rostrally and caudally, respectively, after crossing the midline. These interconnections allow communication between the hemispheres for coordinated activity of these two “separate” hemispheres.

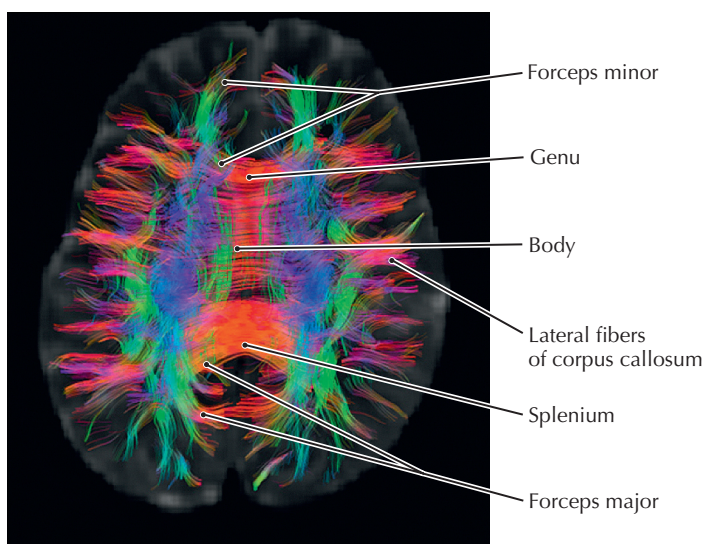




A. Axial view



B. Oblique sagittal view

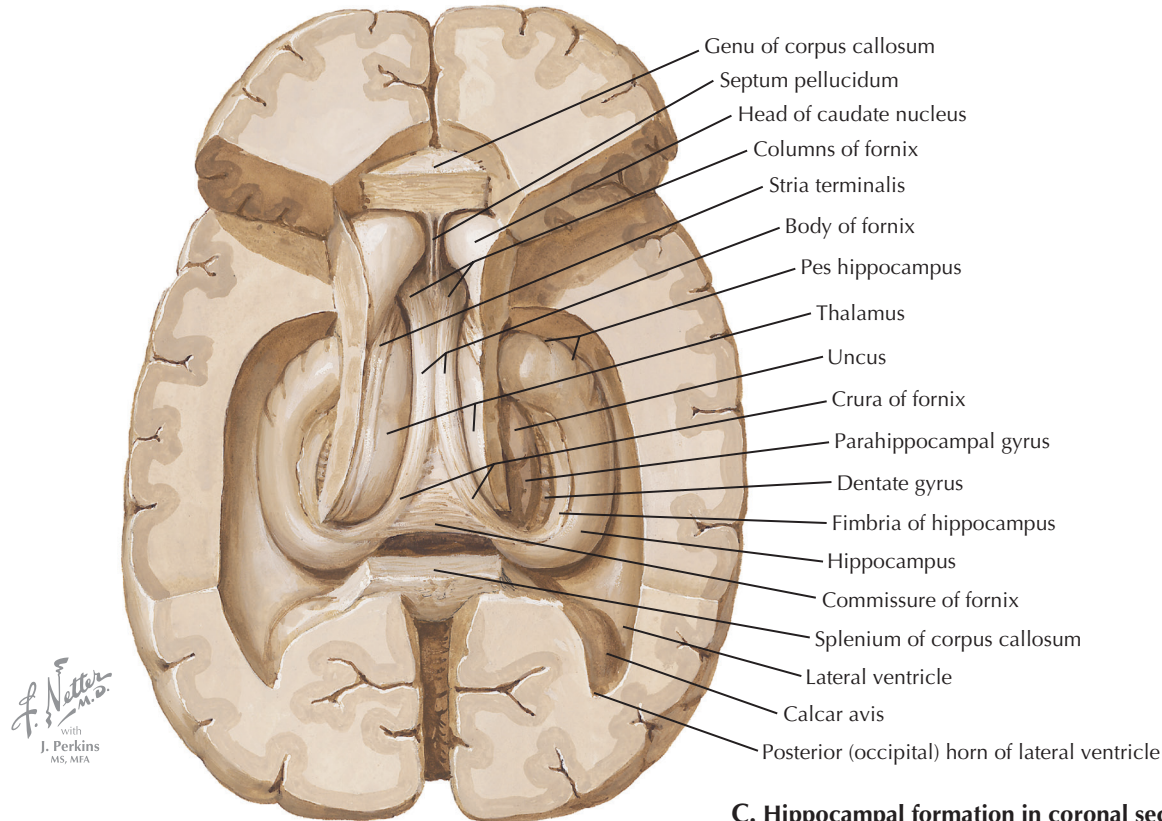
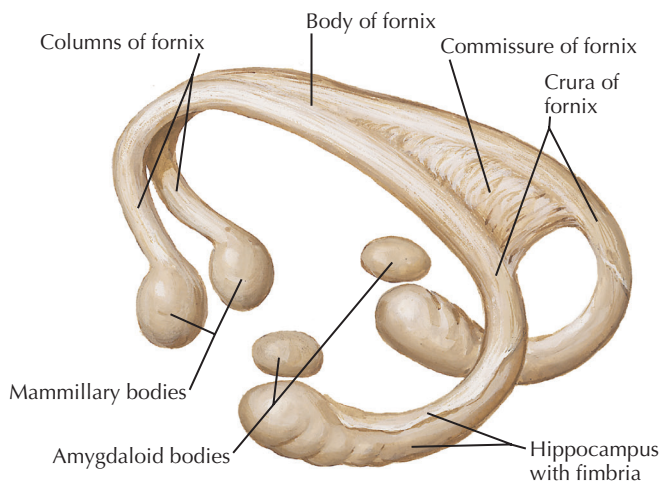
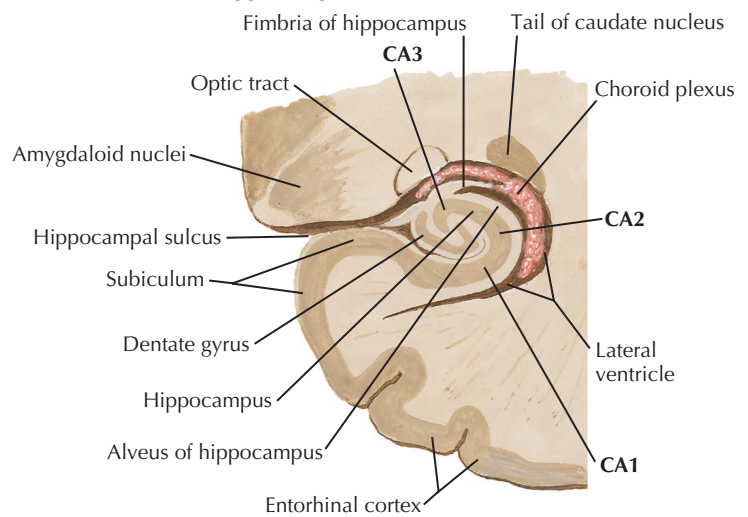


C. Axial view

### 3.16 COLOR IMAGING OF THE CORPUS CALLOSUM BY DIFFUSION TENSOR IMAGING

A-C, Diffusion-weighted imaging (DWI), also called diffusion tensor imaging (DTI), provides unique information about tissue viability, architecture, and cellular function. In many tissues, restricted water diffusion is isotropic or independent of direction. In structured tissues, such as cerebral white matter and peripheral nerves, diffusion is anisotropic because of cellular arrangements. By using diffusion sensitivity that projects in multiple directions, such diffusion can be evaluated in the form of a tensor. Tensor field calculations for six or more diffusion-weighted measurements are based on an

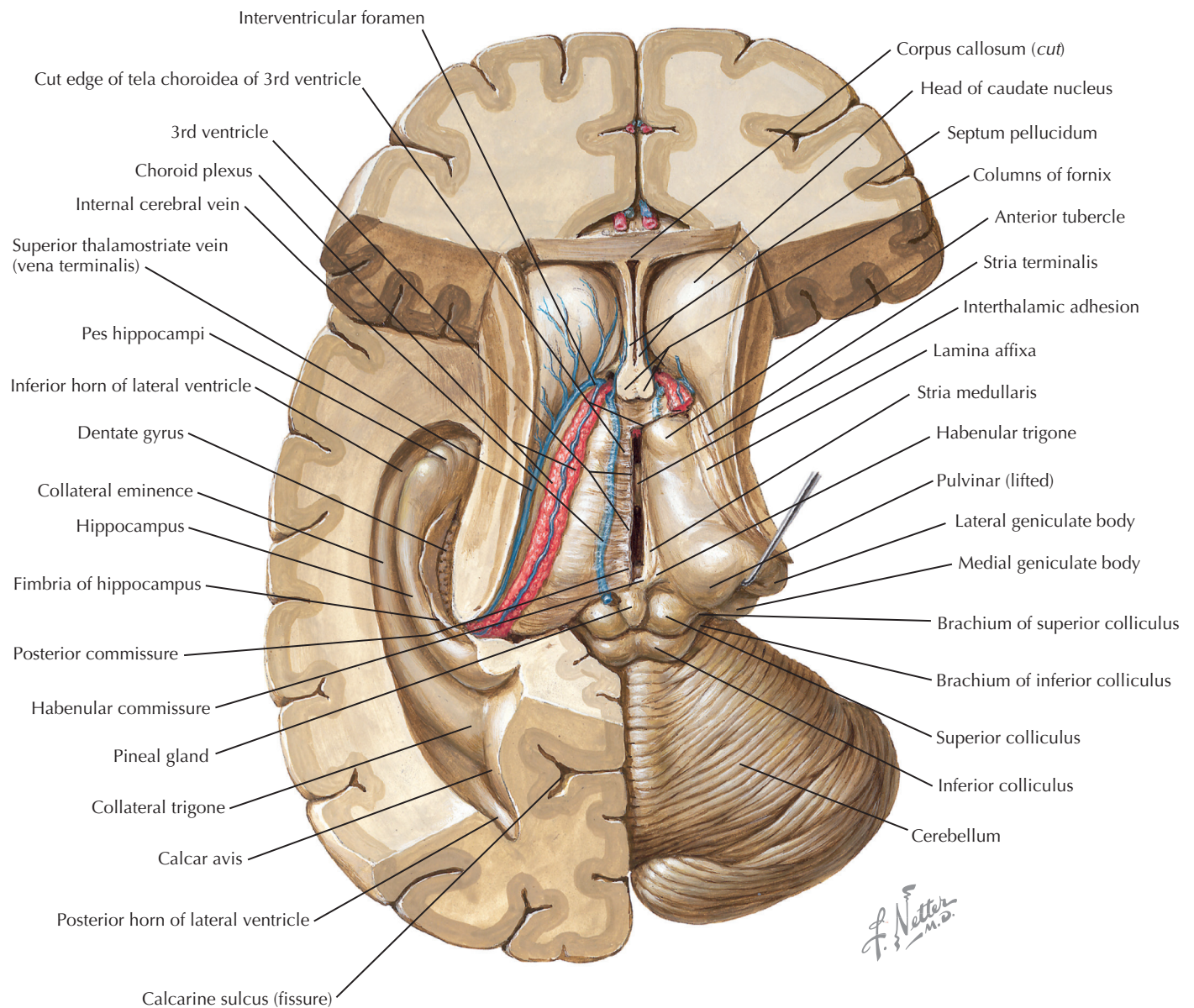
analytical solution of the Stejskal and Tanner diffusion equation system. Diffusion tensor imaging permits reconstruction of axonal tracts in brain and spinal cord; the three-dimensional architecture of the white matter tracts can be traced based on eigenvectors of the diffusion tensor. To discriminate fiber bundles that radiate in different directions, a color scheme is adopted in which green represents eigenvectors pointing in anteroposterior directions; red represents eigenvectors radiating in left-right directions; and blue represents eigenvectors pointing in the superoinferior direction. In these images of the corpus callosum, components of this major commissural bundle are represented in red. See [Video 3-2](#).

**A. Dissection of the hippocampal formation and fornix****B. 3-D Reconstruction of the fornix****C. Hippocampal formation in coronal section****3.17 HIPPOCAMPAL FORMATION AND FORNIX**

In this dissection, the cortex, white matter, and corpus callosum have been removed. The lateral ventricles have been opened, and the head of the caudate nucleus and the thalamus have been dissected away quite close to the midline, allowing a downward view of the full extent of the hippocampal formation, including the dentate gyrus and the associated fornix. This view reveals the relationship between the hippocampus proper and the dentate gyrus. The two limbs of the fornix sweep upward medially, eventually running side by side at their most dorsal position, just beneath the corpus callosum. The full extent of this arching, C-shaped bundle is shown in

the left lower image. The hippocampal formation occupies a large portion of the temporal pole of the lateral ventricle. The dentate gyrus is adjacent to subcomponents of the cornu ammonis (CA) regions of the hippocampus proper (the CA1 and CA3 regions), the subiculum, and the entorhinal cortex). Pyramidal neurons in the CA1 region are particularly sensitive to ischemic damage, and their counterparts in the CA3 region are sensitive to damage from high levels of corticosteroids (cortisol). Damage to pyramidal cells in both regions that has been caused by ischemia and/or high levels of corticosteroids is synergistic.



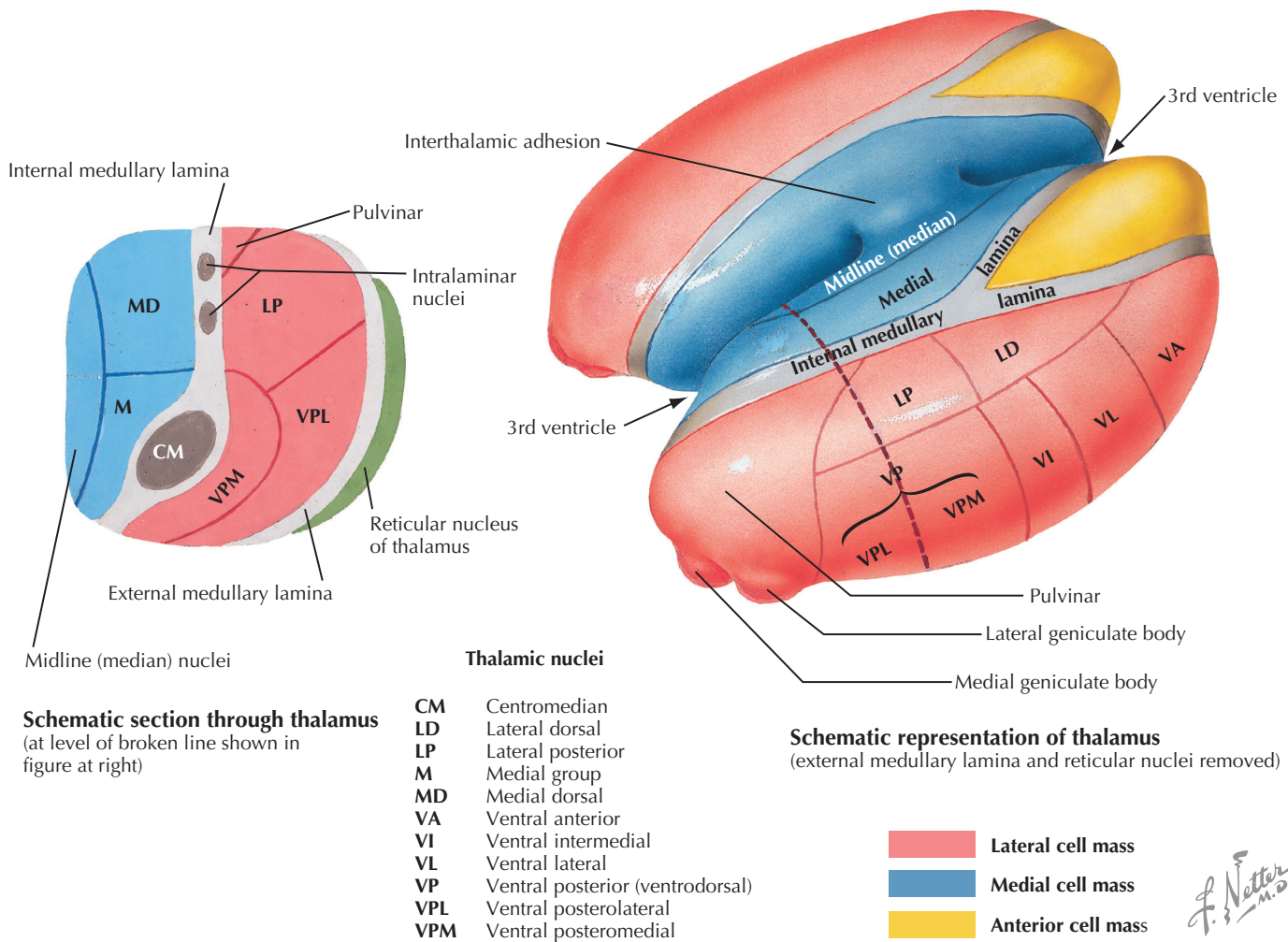


### 3.18 THALAMIC ANATOMY

The thalamus is viewed from above. The entire right side of the brain, just lateral to the thalamus, has been removed, the head of the caudate nucleus has been sectioned, the corpus callosum and all tissue dorsal to the thalamus have been removed, and the third ventricle has been opened from its dorsal surface. The pineal gland is present in the midline, just caudal to the third ventricle; it produces melatonin, a hormone that helps regulate circadian rhythms, sleep, and immune

responses. The superior and inferior colliculi are shown, depicting the dorsal surface of the midbrain. On the left, the temporal horn of the lateral ventricle, with the hippocampal formation, has been exposed to show the relationship of these structures to the thalamus. The terminal vein and choroid plexus accompany the stria terminalis along the lateral margin of the thalamus. The stria medullaris runs along the medial surface of the dorsal thalamus.





### 3.19 THALAMIC NUCLEI

The thalamus is subdivided into nuclear groups (medial, lateral, and anterior) that are separated by medullary (white matter) lamina. Many of these thalamic nuclei are “specific” thalamic nuclei that are reciprocally connected with discrete regions of the cerebral cortex. Some nuclei, such as those embedded within the internal medullary lamina (intralaminar nuclei such as the centromedian and parafascicular nuclei) and the outer, lateral shell nucleus (reticular nucleus of the thalamus), have very diffuse, nonspecific associations with the cerebral cortex.

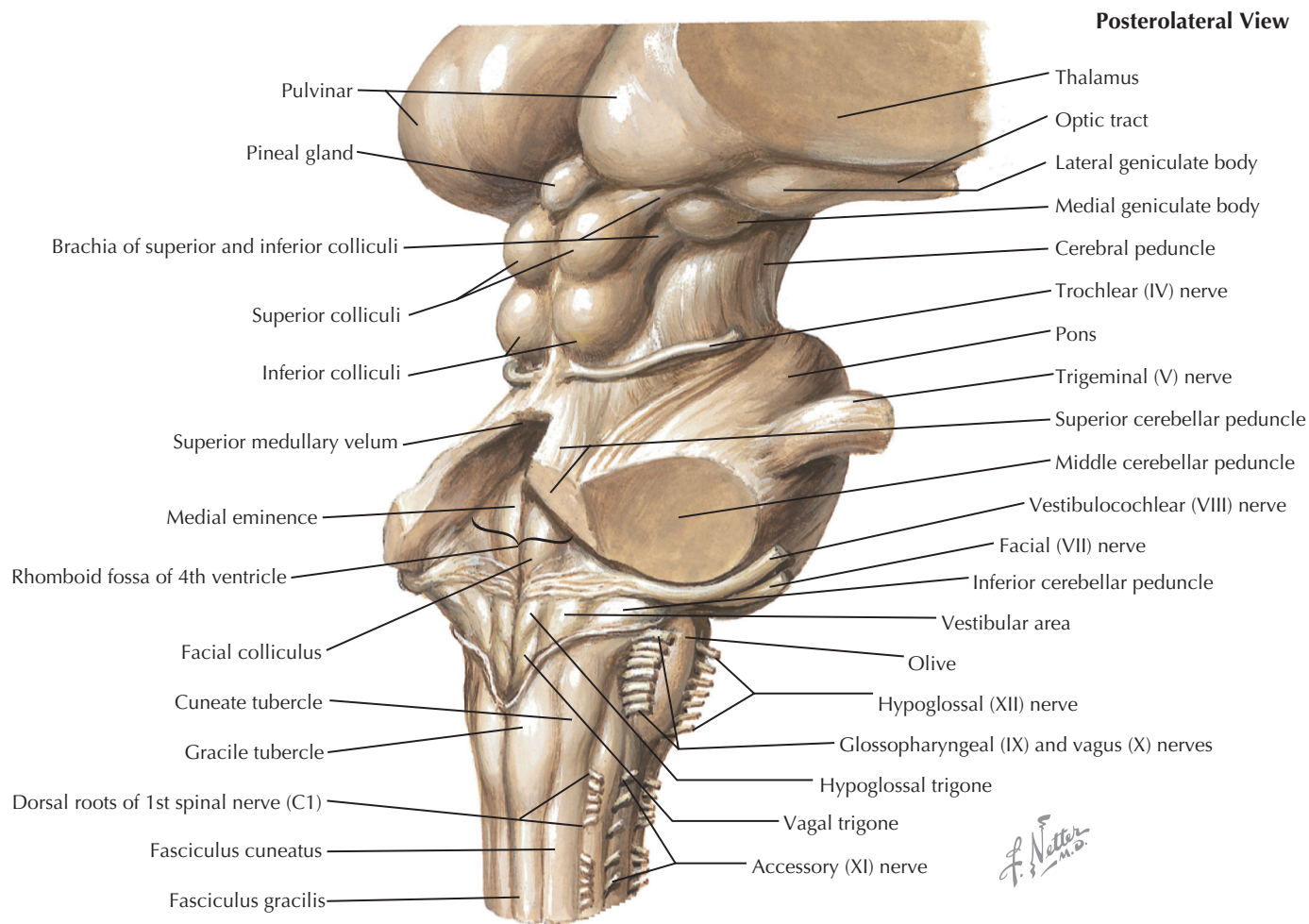
#### CLINICAL POINT

Thalamic syndrome (posterolateral thalamic syndrome, or Dejerine-Roussy syndrome) results from obstruction of the thalamogeniculate arterial supply to the region of the thalamus where the ventroposterolateral nucleus is located. Initially, all sensation is lost in the contralateral body, epicritic more completely than protopathic. Commonly, severe spontaneous pain occurs contralaterally, described as stabbing, burning, or tearing pain; it is diffuse and persistent. Even light stimulation can evoke such pain (hyperpathia), and other sensory stimuli or emotionally charged situations can result in these painful sensations. Even when the threshold for pain and temperature sensation (protopathic sensations) is elevated, the thalamic pain may be present; it is called analgesic dolorosa. If the vascular lesion includes the subthalamic nucleus or associated basal ganglia circuitry, the patient may also experience hemiballismus (or choreoform or athetoid) movements in addition to the sensory deficits.

# 4

## BRAIN STEM AND CEREBELLUM

- 4.1 [Brain Stem Surface Anatomy: Posterolateral View](#)
- 4.2 [Brain Stem Surface Anatomy: Anterior View](#)
- 4.3 [Cerebellar Anatomy: External Features](#)
- 4.4 [Cerebellar Anatomy: Internal Features](#)



#### 4.1 BRAIN STEM SURFACE ANATOMY: POSTEROLATERAL VIEW

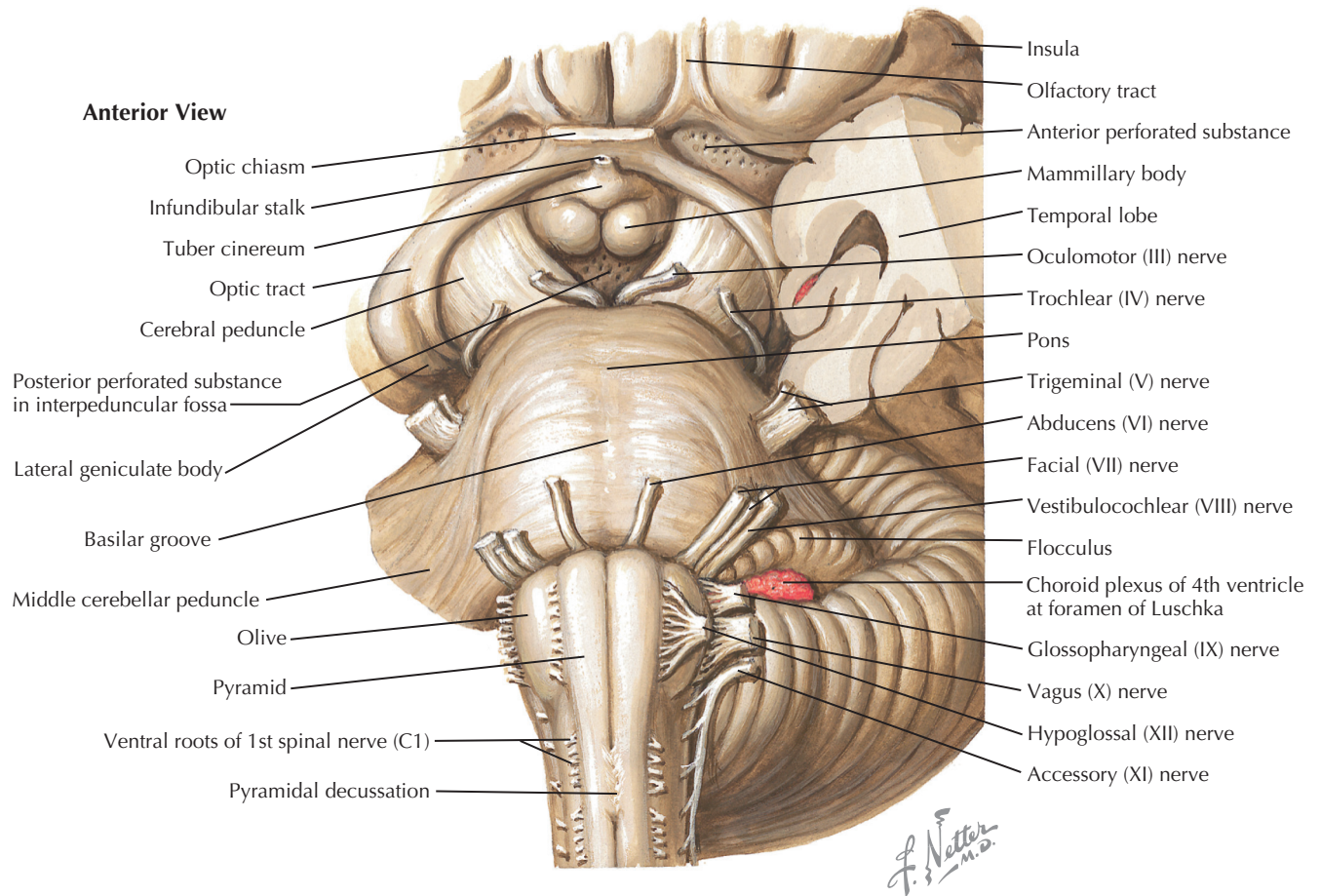
The entire telencephalon, most of the diencephalon, and the cerebellum are removed to reveal the dorsal surface of the brain stem. The three cerebellar peduncles (superior, middle, and inferior) are sectioned and the cerebellum removed. The dorsal roots provide input into the spinal cord, and the cranial nerves provide input into and receive output from the brain stem. The fourth nerve (trochlear) is the only cranial nerve to exit dorsally from the brain stem. The tubercles and trigones on the floor of the fourth ventricle are named for nuclei just beneath them. The superior and inferior colliculi form the dorsal surface of the midbrain, and the medial and lateral geniculate bodies (nuclei), associated with auditory and visual processing, respectively, are shown at the caudalmost region of the diencephalon.

#### CLINICAL POINT

The facial colliculus is an elevation on the floor of the fourth ventricle in the pons under which is located the abducens nucleus (cranial nerve VI) and the axons of the facial nerve nucleus (VII), which arc around the abducens nucleus. A tumor or other lesion on one side of the floor of the fourth ventricle may induce symptoms related to cranial nerves VI and VII, including (1) ipsilateral paralysis of lateral gaze (lateral rectus) and medial gaze (resulting from damage to interneurons of the abducens nucleus, whose axons ascend to the nucleus of CN III via the medial longitudinal fasciculus); and (2) ipsilateral facial palsy resulting from damage to the axons in the genu of the facial nerve.

The cerebellar peduncles convey the cerebellar afferent and efferent fibers. The superior peduncle conveys the major efferents to the red nucleus and thalamus (especially the ventrolateral nucleus), whereas the inferior peduncle conveys the major efferents to the vestibular and reticular nuclei. The middle peduncle conveys the cortico-ponto-cerebellar fibers. Afferents enter the cerebellum especially through the inferior peduncle but also through the superior peduncle. Damage to the lateral hemisphere of the cerebellum or its associated peduncles results in ipsilateral symptoms, including limb ataxia, mild hypotonia, dysmetria (misjudgment of distance), decomposition of movement (especially movement involving several joints), intention tremor (with movement), dysdiadochokinesia (inability to perform rapid alternating movements), and inability to dampen movements appropriately (rebound phenomena).





## 4.2 BRAIN STEM SURFACE ANATOMY: ANTERIOR VIEW

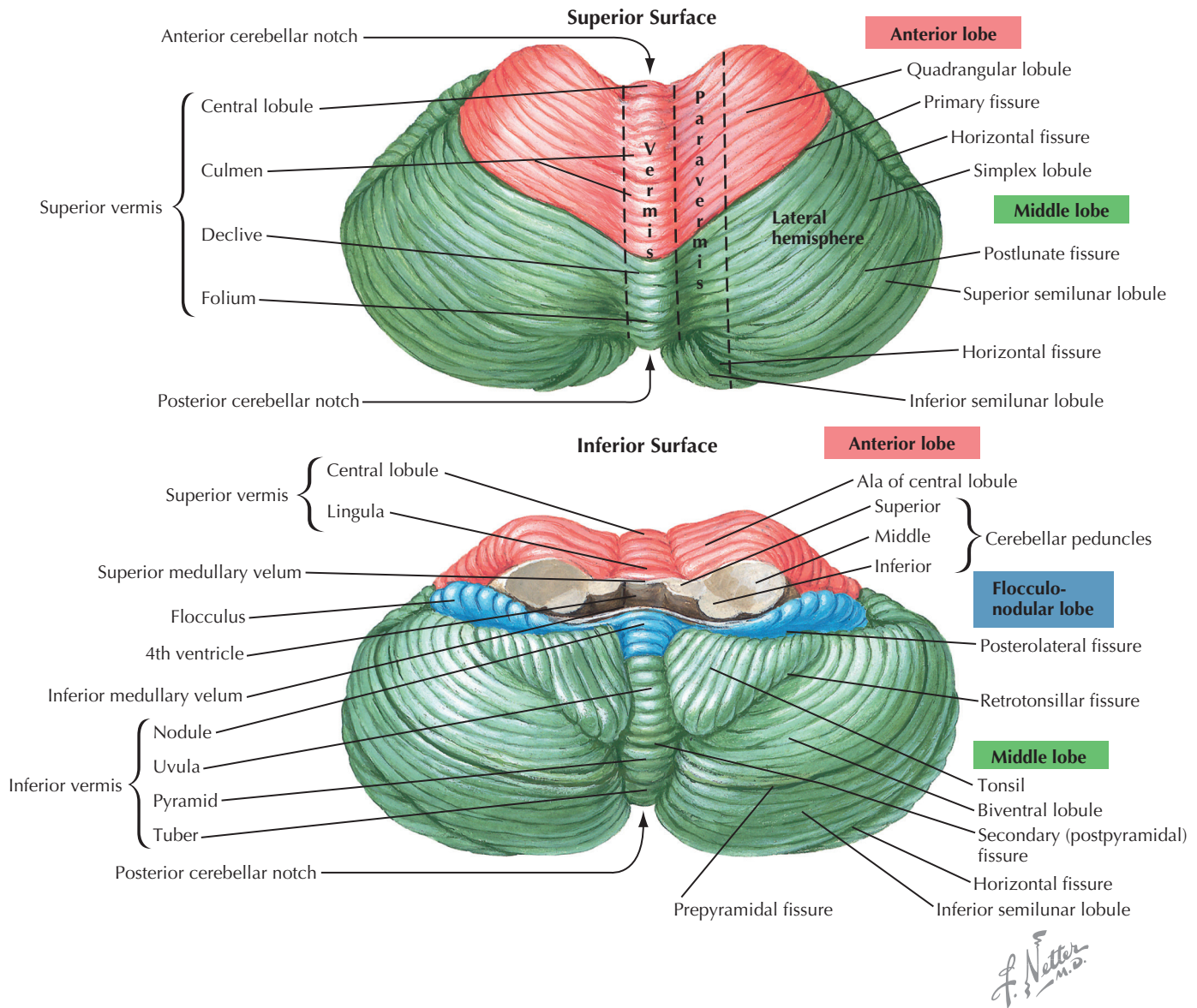
The left temporal lobe is dissected to show the anterior (ventral) surface of the brain stem. The cerebral peduncles, direct caudal extensions of the posterior limbs of the internal capsules, carry corticospinal and corticobulbar fibers from the internal capsule to the spinal cord and brain stem, respectively. The decussation of the pyramids marks the boundary between the caudal medulla and the cervical spinal cord. Cranial nerve XI (accessory) is associated with the lateral margin of the upper cervical spinal cord. Cranial nerves XII (hypoglossal), X (vagus), and IX (glossopharyngeal) emerge from the ventrolateral margin of the medulla. Cranial nerves VI (abducens), VII (facial), and VIII (vestibulocochlear) emerge from the boundary between the medulla and the pons. Cranial nerve V (trigeminal) emerges from the lateral margin of the upper pons. Cranial nerve III (oculomotor) emerges from the interpeduncular fossa in the medial portion of the caudal midbrain. The optic nerve, chiasm, and tract (cranial nerve II) and the olfactory tract (cranial nerve I) are not peripheral nerves; they are central nervous system tracts that were identified as cranial nerves by anatomists in centuries past.

### CLINICAL POINT

The oculomotor nerve (III) emerges from the ventral surface of the brain stem in the interpeduncular fossa, at the medial edge of the

cerebral peduncle. In conditions of increased intracranial pressure in the anterior and middle cranial fossa, such as that caused by a tumor, edema from injury, or other space-occupying lesions, the brain stem can herniate through the tentorium cerebelli, a rigid wing of dura. The resultant transtentorial herniation can compress the third nerve on one side (ipsilateral fixed and dilated pupil resulting from parasympathetic disruption; and paralysis of medial gaze resulting from motor fiber disruption) and compress the cerebral peduncle on that same side, resulting in contralateral hemiparesis.

The medullary pyramids contain the descending corticospinal tract fibers from the ipsilateral cerebral cortex, particularly from the motor and premotor cortex. The major crossing of the corticospinal tract takes place in the decussation of the pyramids (80%), producing the crossed, descending, lateral corticospinal tract in the spinal cord. An infarct in the upper reaches of the anterior spinal artery or the paramedian branches of the vertebral artery can result in damage to the ipsilateral pyramid (contralateral hemiparesis); to the ipsilateral medial lemniscus (contralateral loss of epicritic somatosensory sensations such as fine, discriminative touch, vibratory sensation, and joint position sense); and the ipsilateral hypoglossal nerve (cranial nerve XII; paralysis of the ipsilateral tongue, which deviates toward the weak side when protruded). This condition is called Dejerine's syndrome. The hemiparesis is not spastic and is characterized by mild loss of tone, loss of fine hand movements, and a plantar extensor response (Babinski's sign). It appears that isolated damage to the pyramids does not result in spasticity. Damage to other descending systems, from either the motor-related cortices or other upper motor neurons in the brain stem, must accompany pyramidal tract damage to produce spasticity. Thus, the term *pyramidal tract syndrome*, when used to describe spastic hemiplegia, is a misnomer and is anatomically incorrect.



### 4.3 CEREBELLAR ANATOMY: EXTERNAL FEATURES

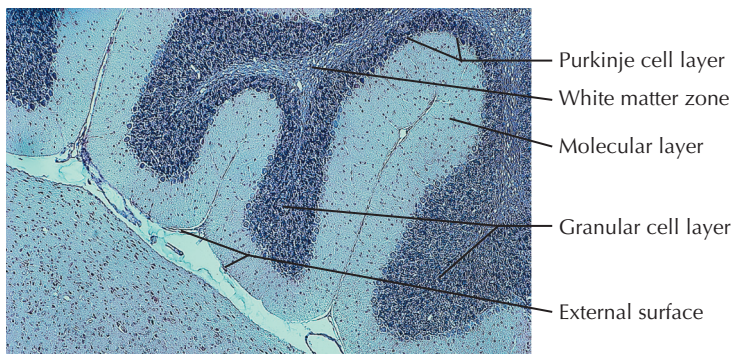
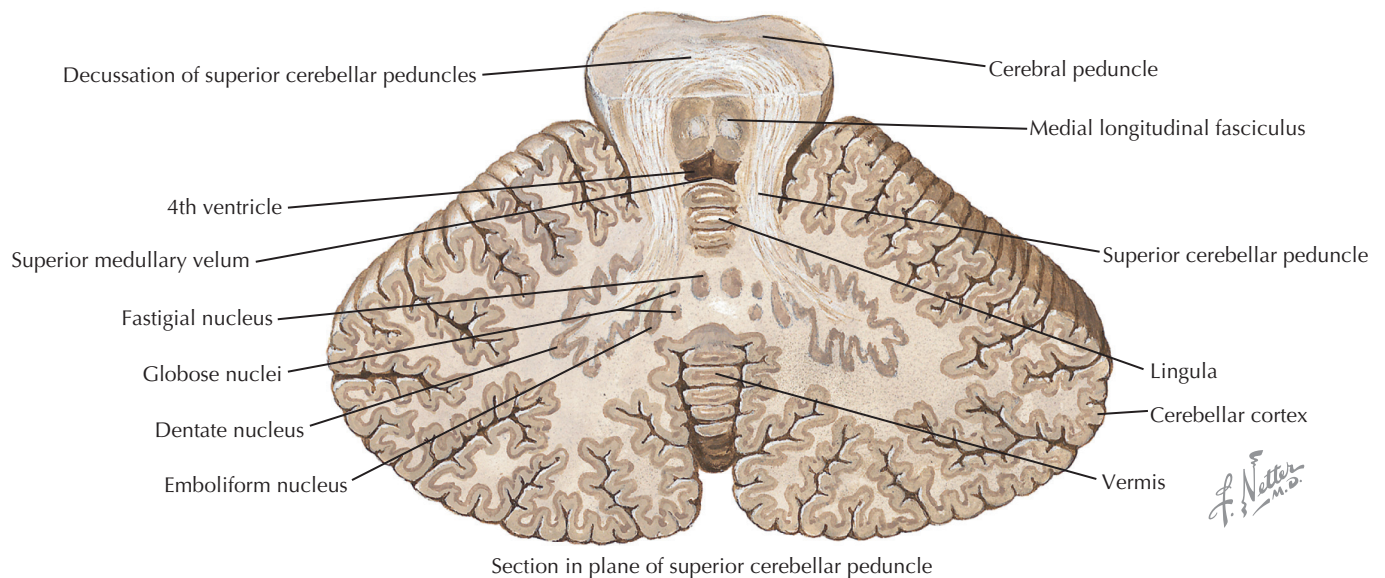
These color-coded illustrations show the superior (dorsal) surface and the inferior (ventral) surface of the cerebellum. The cerebellar peduncles are cut to provide this view. The ventral surface of the cerebellum is the roof of the fourth ventricle. The anterior, middle, and flocculo-nodular lobes of the cerebellum are traditional anatomic subdivisions with well-described syndromes derived from lesions. The vermis, paravermis, and lateral hemispheres are cerebellar cortical zones that have specific projection relationships with deep cerebellar nuclei (vermis with fastigial nucleus and lateral vestibular nucleus; paravermis with globose and emboliform nuclei; lateral hemispheres with dentate nucleus) which, in turn, provide neuronal feedback to specific upper motor neuronal systems that regulate specific types of motor responses. These relationships are key to understanding how the major

upper motor neuronal systems are coordinated for specific functional tasks.

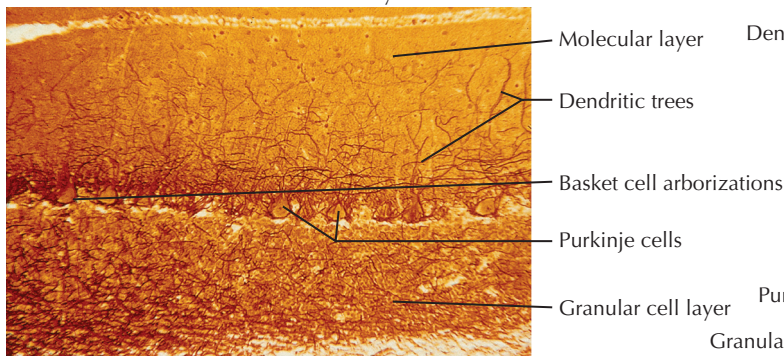
#### CLINICAL POINT

The anterior lobe of the cerebellum (paleocerebellum) receives extensive input from the proprioceptors of the body, particularly the limbs, via the spinocerebellar tracts. This region is particularly important for coordination of the lower limbs. The anterior cerebellum also helps to regulate tone in the limbs via connections to the lateral vestibular nucleus. In some alcoholic patients, the anterior lobe of the cerebellum shows selective cortical degeneration. The patient shows a wide-based stance and gait with some ataxia but little involvement of dysarthria or oculomotor dysfunction. The gait tends to be stiff-legged, probably reflecting disinhibition of the extensor-dominant lateral vestibular nucleus. Typically, heel to shin testing is not severely impaired when the patient is tested while lying down. Few treatment options are available.

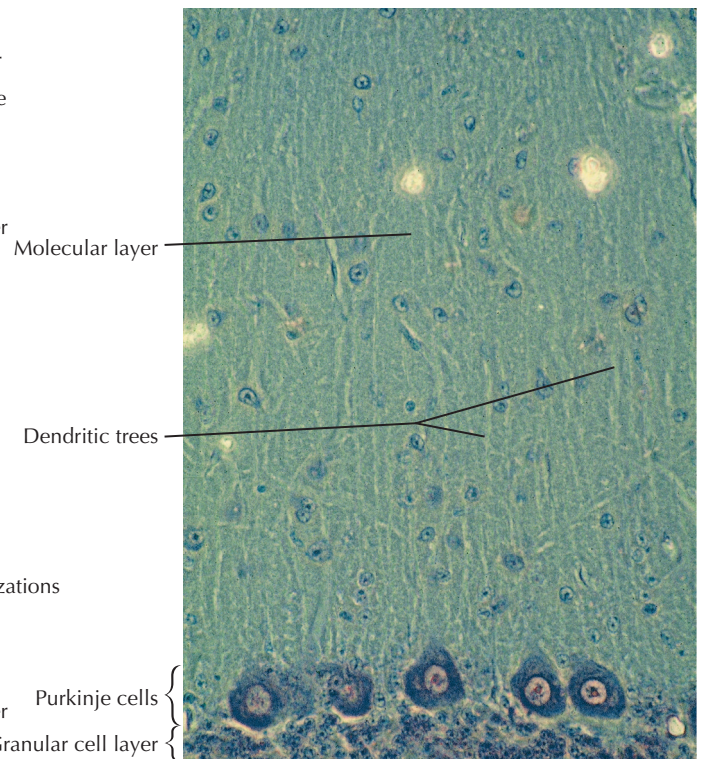




Cerebellar architecture. The infolding of cerebellar folia demonstrates the architecture of the cerebellar cortex. Cresyl violet stain.



Cerebellar cortex. Purkinje cells with their huge planar dendritic trees arborizing into the molecular layer. Basket cell arborizations surrounding the Purkinje cell bodies. Granular cell layer with granule cells and Golgi cells. The molecular layer contains outer stellate cells and basket cells. Cajal stain- fiber stain.



Cerebellar cortex. Purkinje cells send their dendritic trees into the molecular layer. Densely-packed granule cells sit deep to the Purkinje cells in the granular layer. Cresyl violet stain with phase contrast microscopy.

#### 4.4 CEREBELLAR ANATOMY: INTERNAL FEATURES

The major internal subdivisions of the cerebellum are shown in this transverse section. The outer zone, the cerebellar cortex (three-layered), is infolded to form numerous folia. Deep to the folia is the white matter, carrying afferent and efferent fibers associated with the cerebellar cortex. Deep to the white matter are the deep cerebellar nuclei, cell groups that receive most of the output from the cerebellar cortex via Purkinje cell axon projections. The deep cerebellar nuclei also receive

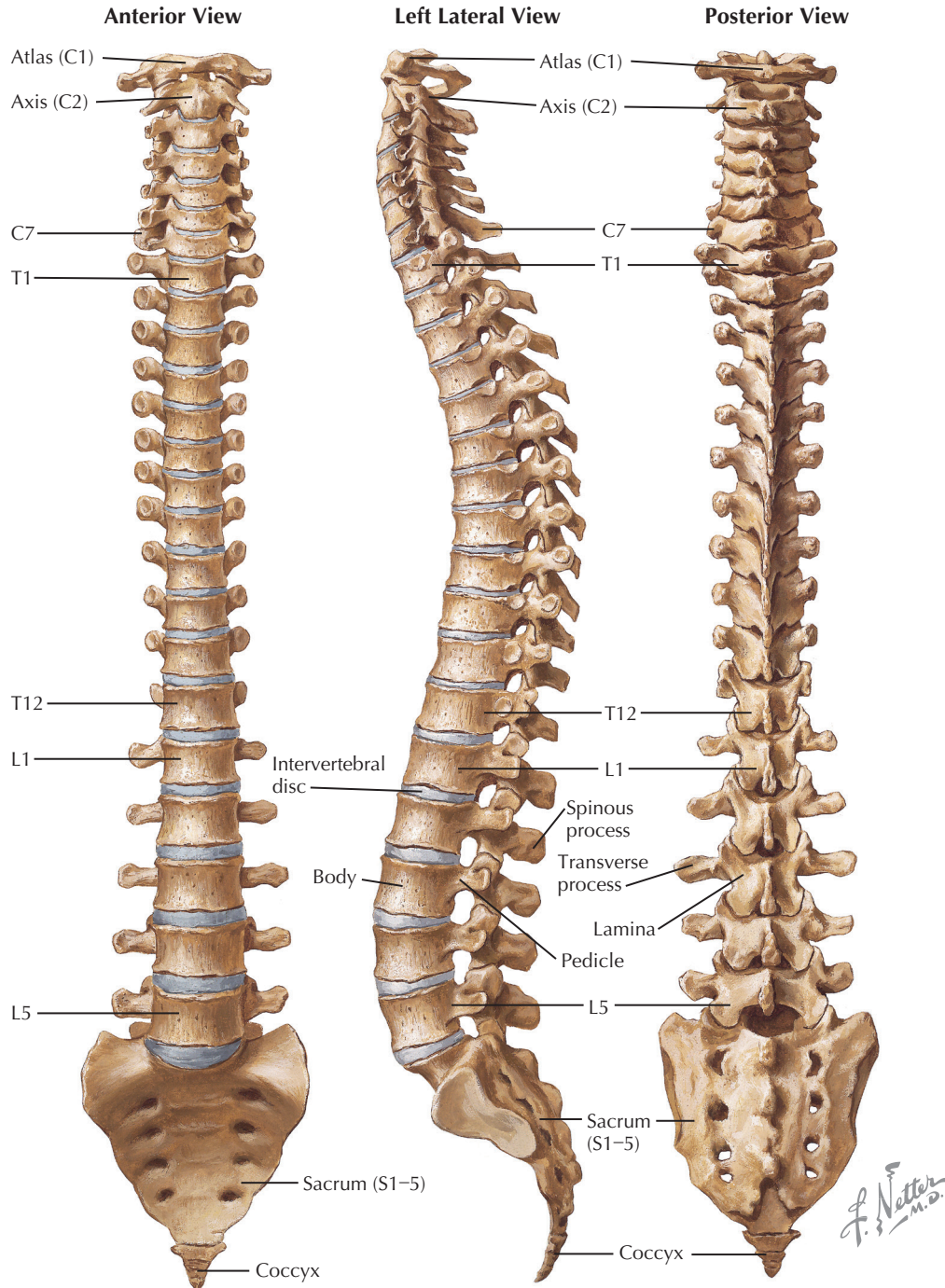
collaterals from mossy fiber and climbing fiber inputs to the cerebellum. These direct afferent inputs to the deep nuclei provide a coarse adjustment for their output to upper motor neurons, whereas the loop of afferent input through the cerebellar cortex back to the deep nuclei provides fine adjustments for their output to upper motor neurons. The cerebellar peduncles are interior to the deep nuclei; these massive fiber bundles interconnect the cerebellum with the brain stem and the thalamus.



# 5

## SPINAL CORD

- 5.1 Spinal Column: Bony Anatomy
- 5.2 Lumbar Vertebrae: Radiography
- 5.3 Spinal Cord: Gross Anatomy in Situ
- 5.4 The Spinal Cord: Its Meninges and Spinal Roots
- 5.5 Spinal Cord: Cross-Sectional Anatomy in Situ
- 5.6 Spinal Cord: White and Gray Matter

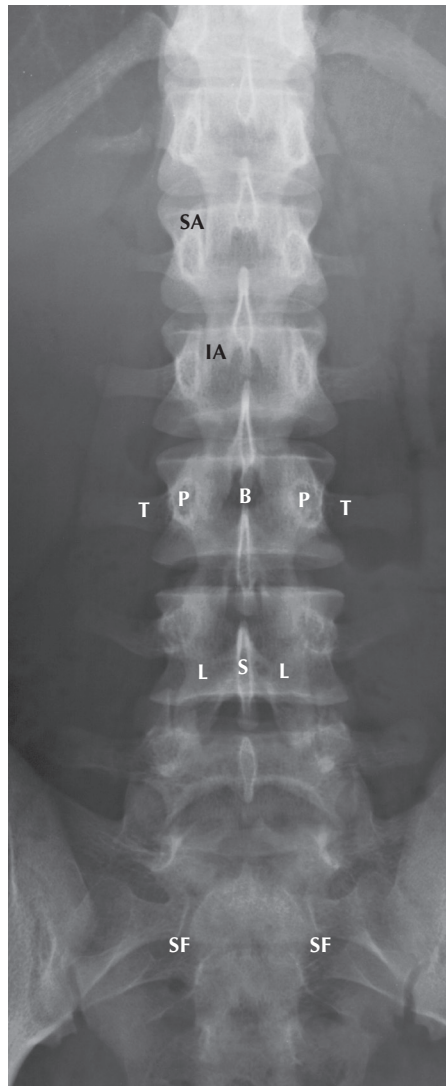


### 5.1 SPINAL COLUMN: BONY ANATOMY

Anterior, lateral, and posterior views of the bony spinal column show the relationships of the intervertebral discs with the vertebral bodies. The discs' proximity to the intervertebral foramina provides an anatomical substrate for understanding the possible impingement of a herniated nucleus pulposus on

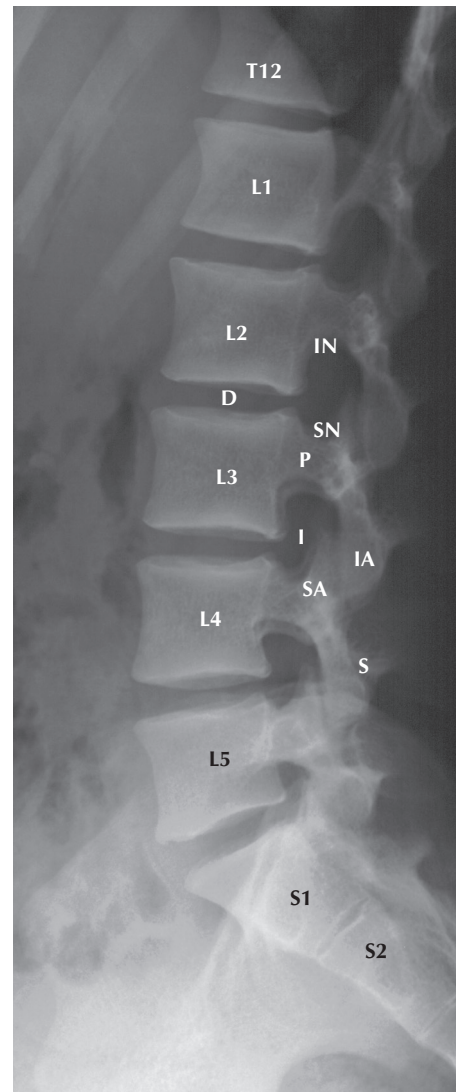
spinal roots. Such impingement can cause excruciating, radiating pain if dorsal roots are involved and can cause loss of motor control of affected muscles if ventral roots are involved. In the adult, the spinal cord extends caudally only as far as the L1 vertebral body, leaving the lumbar cistern (the subarachnoid space) accessible for withdrawal of cerebrospinal fluid.

Anteroposterior Radiograph



- B** Body of L3 vertebra
- IA** Inferior articular process of L1 vertebra
- L** Lamina of L4 vertebra
- P** Pedicle of L3 vertebra
- S** Spinous process of L4 vertebra
- SA** Superior articular process of L1 vertebra
- SF** Sacral foramen
- T** Transverse process of L3 vertebra

Lateral Radiograph



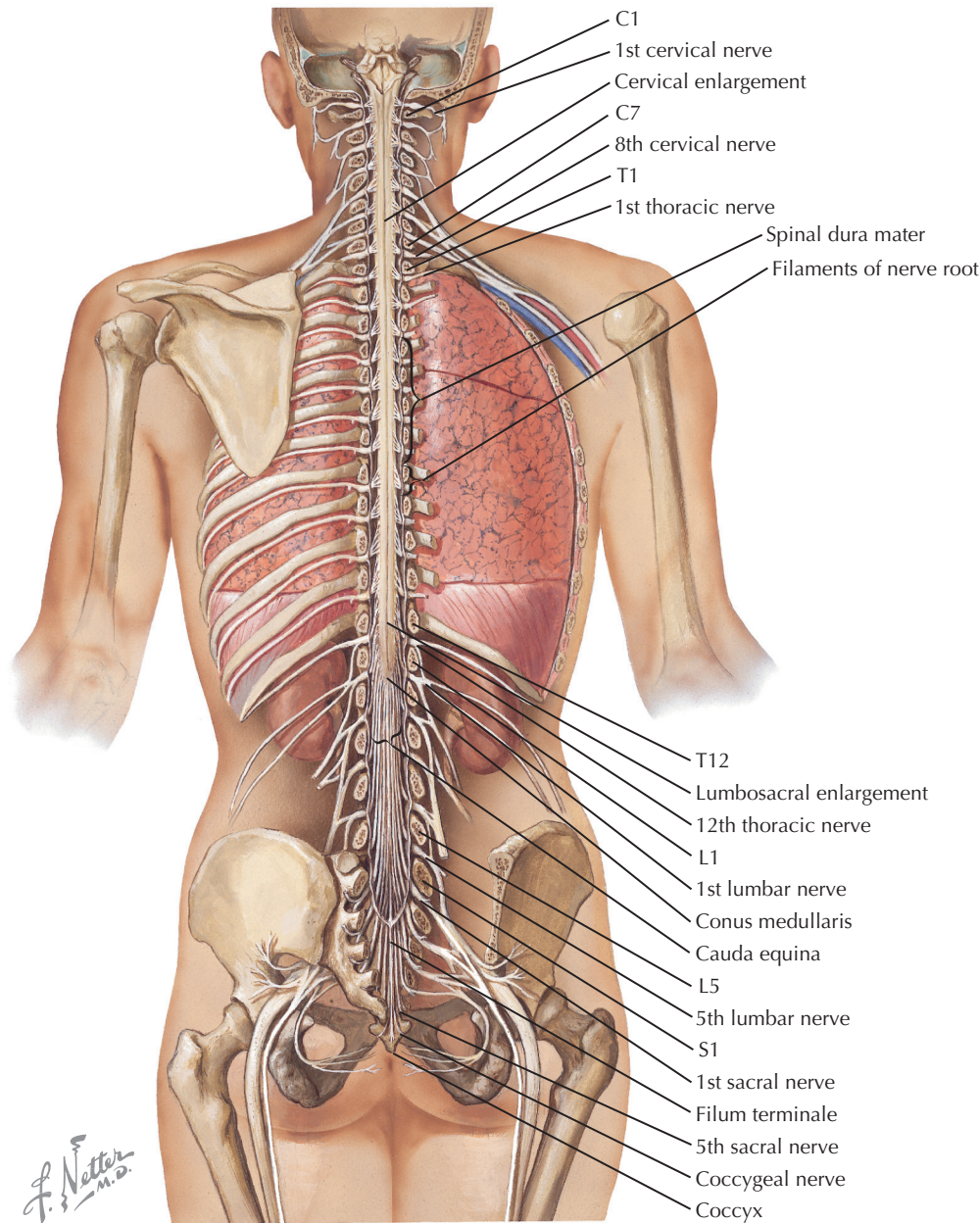
- D** Intervertebral disc space
  - I** Intervertebral foramen
  - IA** Inferior articular process of L3 vertebra
  - IN** Inferior vertebral notch of L2 vertebra
  - P** Pedicle of L3 vertebra
  - S** Spinous process of L4 vertebra
  - SA** Superior articular process of L4 vertebra
  - SN** Superior vertebral notch of L3 vertebra
- Note:** The vertebral bodies are numbered

## 5.2 LUMBAR VERTEBRAE: RADIOGRAPHY

These lumbar radiographs show the lumbar spine in an anteroposterior view and a lateral view. The vertebral bodies, with their spinous and transverse processes, are visible, and the spaces occupied by the intervertebral discs are uniform

and symmetrical in a normal radiograph. A herniated disc may show a disruption of that symmetry. However, the presence of lumbar radiculopathy and a herniated disc is not always accompanied by radiographic abnormalities.





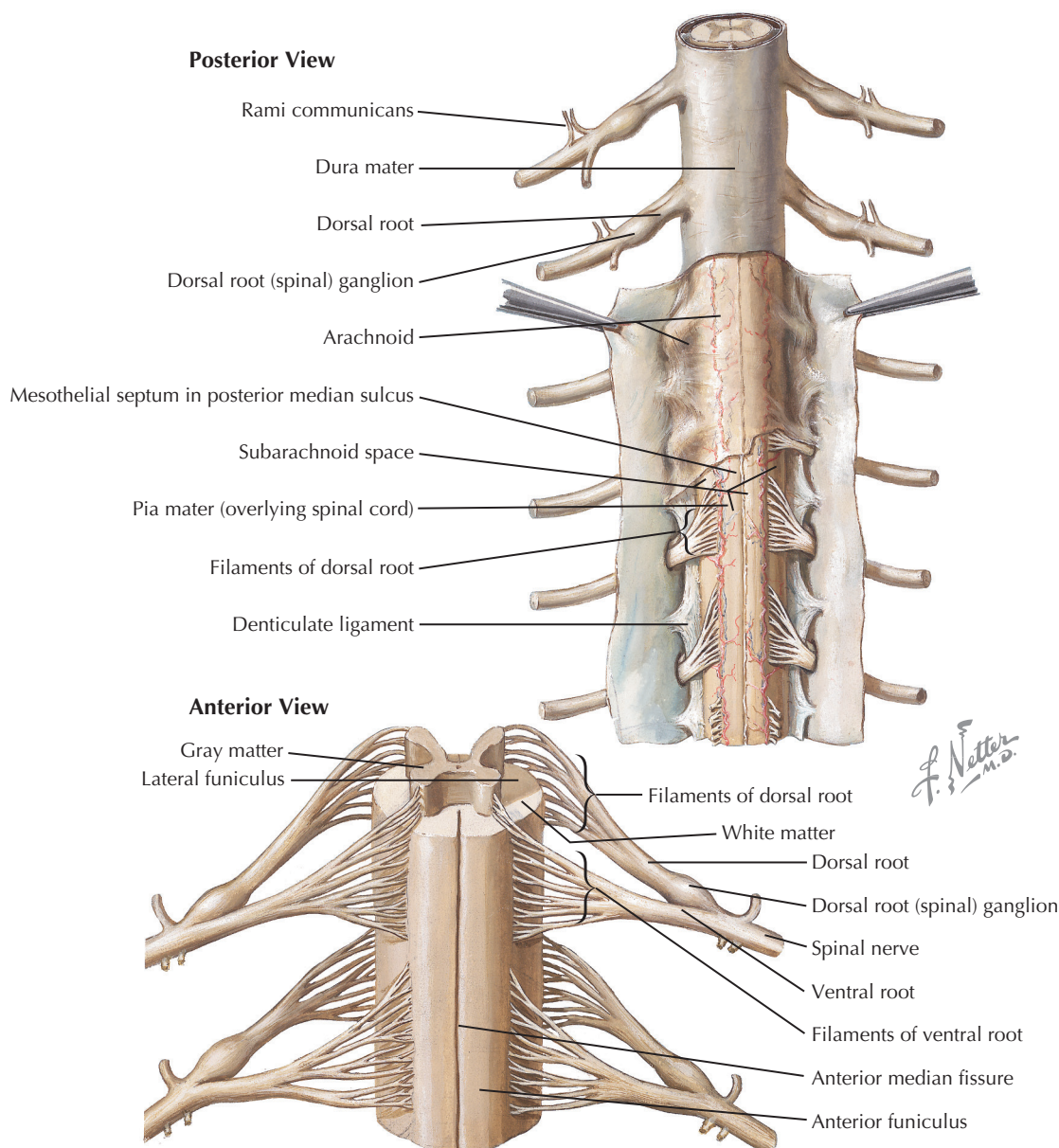
### 5.3 SPINAL CORD: GROSS ANATOMY IN SITU

The posterior portions of the vertebrae have been removed to show the posterior (dorsal) surface of the spinal cord. Cervical and lumbosacral enlargements of the spinal cord reflect innervation of the limbs. The spinal cord extends rostrally through the foramen magnum, continuous with the medulla. The conus medullaris is located under the L1 vertebral body. The longitudinal growth of the spinal column exceeds that of the spinal cord, causing the spinal cord to end considerably more rostrally in the adult than in the newborn. The associated nerve roots traverse a considerable distance through the subarachnoid space, particularly more caudally in the lumbar cistern, to reach the appropriate intervertebral foramina of exit. In the lumbar cistern, this collection of nerve roots is called the cauda equina (horse's tail). The lumbar cistern is a large reservoir of subarachnoid space from which cerebrospi-

nal fluid can be withdrawn. The filum terminale helps to anchor the spinal cord caudally to the coccyx.

#### CLINICAL POINT

In the adult, the spinal cord ends at the level of the L1 vertebral body, and the roots extend caudally in the cauda equina to exit in the appropriate intervertebral foramina. As a consequence, a large lumbar cistern is filled with cerebrospinal fluid (CSF); from this cistern, samples can be drawn in a spinal tap with little risk for neurological damage by the needle. Analysis of CSF is a vitally important part of neurological assessment in many conditions, such as infections, bleeds, inflammatory conditions, some degenerative conditions, and other disorders. The CSF is commonly analyzed for color and appearance, viscosity, cytology, and the presence of red and white blood cells, protein, and glucose. It should be noted that in some conditions in which intracranial pressure is elevated, withdrawal of CSF from the lumbar cistern may encourage brain stem herniation through the foramen magnum.



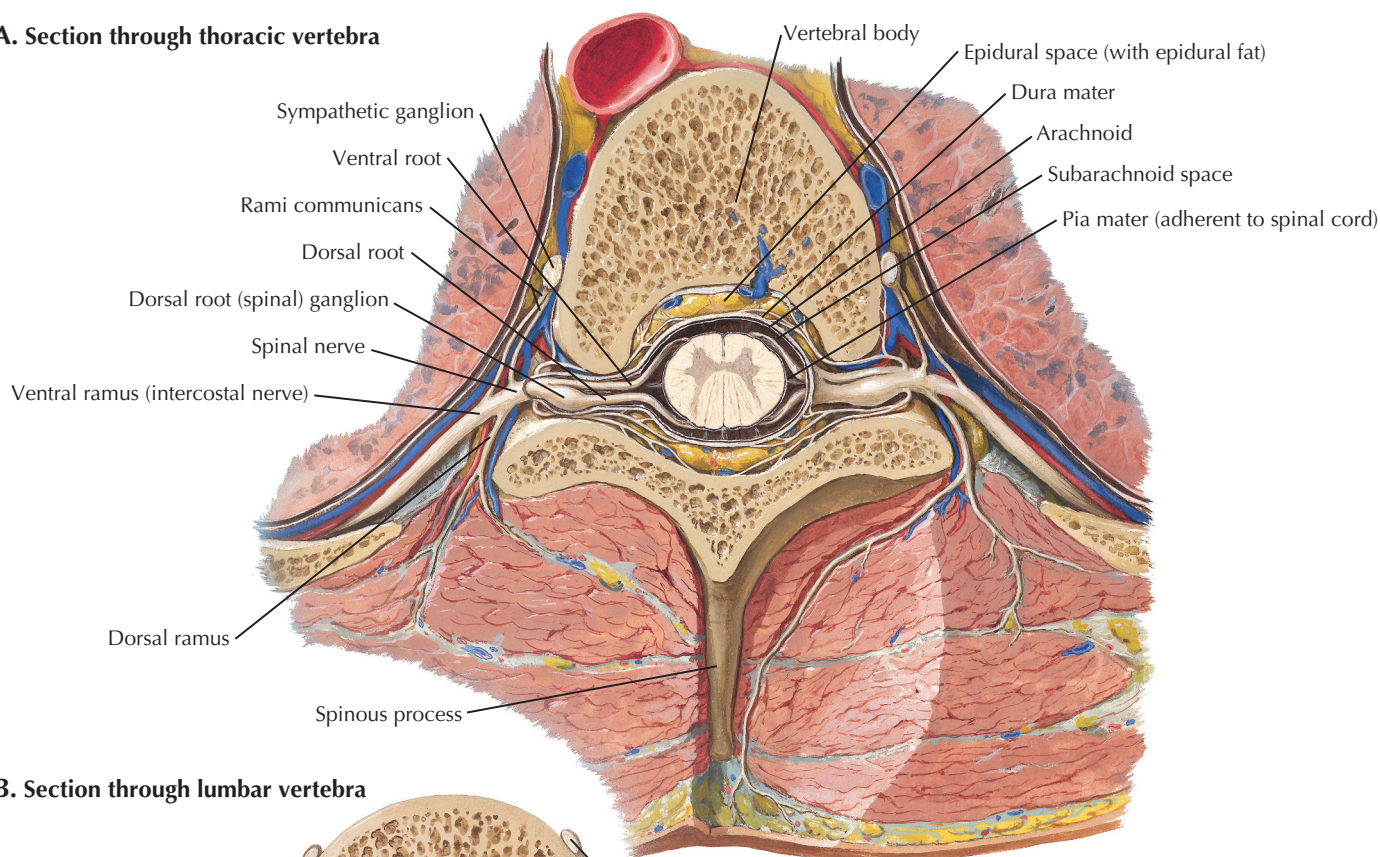
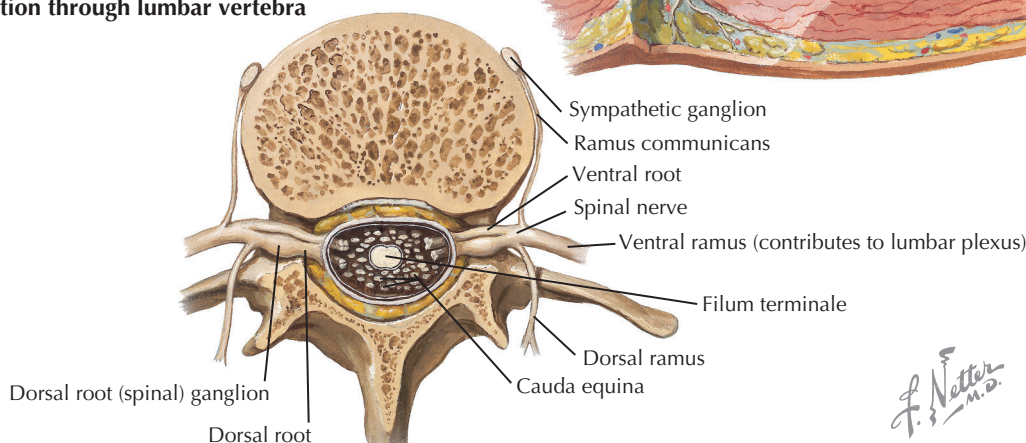
#### 5.4 THE SPINAL CORD: ITS MENINGES AND SPINAL ROOTS

The upper illustration is a posterior (dorsal) view of the spinal cord showing both intact and reflected meninges. The pia adheres to every contour of the spinal cord surface. The arachnoid membrane extends over these contours and adheres to the overlying dura, a very tough, fibrous, and protective membrane. These meninges extend outward to the nerve roots. The denticulate ligaments are fibrous structures that help to anchor the spinal cord in place. The posterior spinal arteries supply the dorsal spinal cord with blood and run just medial to the dorsal root entry zone. The lower illustration shows an anterior (ventral) view of the spinal cord with the meninges stripped away. Both the dorsal and the ventral roots consist of a convergence of rootlets that provide a continuous dorsal and ventral array of rootlets along the entire longitudinal extent of the spinal cord.

#### CLINICAL POINT

Groups of contiguous dorsal and ventral spinal rootlets converge to form the major dorsal and ventral roots associated with each level of the spinal cord. Herniation of an intervertebral disc, usually resulting from a flexion injury, may cause the nucleus pulposus to extrude in a posterolateral direction and impinge on a dorsal root. The L5–S1 and L4–L5 discs are most commonly involved in the lower extremities, and the C6–C7, C5–C6, and C4–C5 discs in the upper extremities. Sharp, radiating pain in the territory of the nerve root is the most common symptom. In some disc herniations, a specific muscle-stretch reflex may be absent or diminished. When there is compression of a dorsal root, there will not be a corresponding nerve root territory in which anesthesia is present, unlike in a branch lesion of the trigeminal nerve; the dorsal roots send sensory axons to at least three dermatomal segments and have sufficient overlap that an isolated root lesion is unlikely to produce complete anesthesia in that territory. Compression of a ventral root because of disc herniation is less common than that of a dorsal root; it may be accompanied by significant weakness in the muscles supplied by that ventral root.



**A. Section through thoracic vertebra****B. Section through lumbar vertebra****5.5 SPINAL CORD: CROSS-SECTIONAL ANATOMY IN SITU**

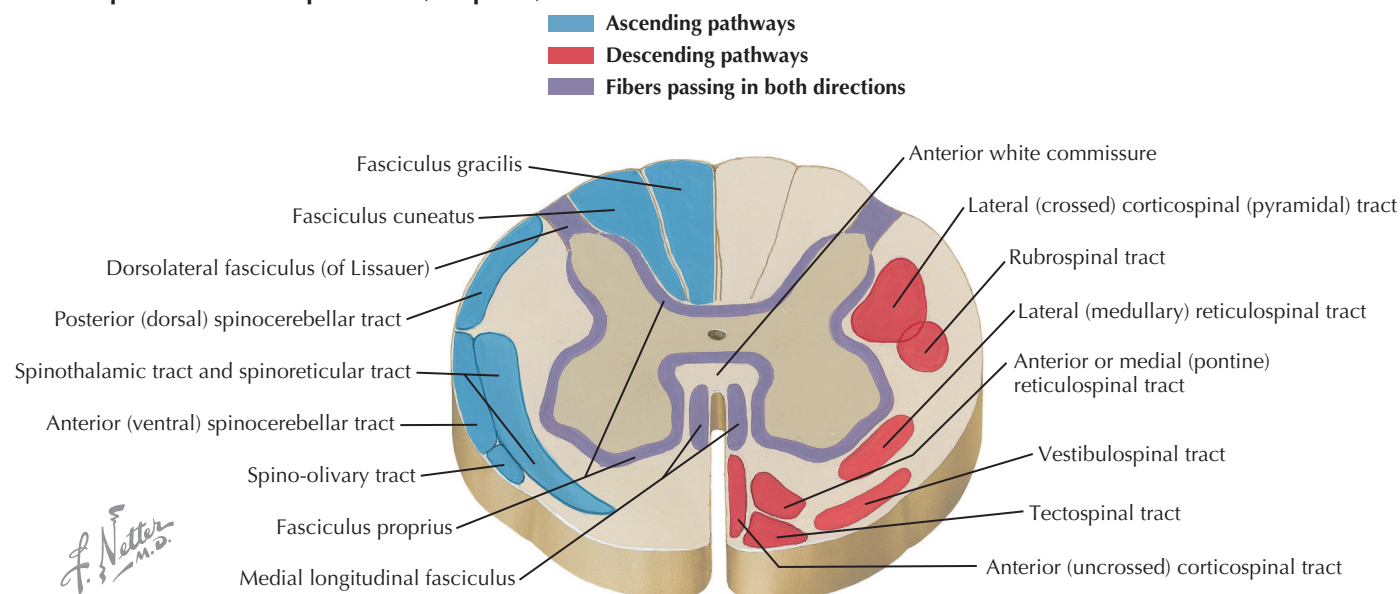
**A,** The spinal cord in the spinal canal is surrounded by meninges. Dorsal and ventral roots course through the intervertebral foramina. The epidural space, with its associated fat, is sometimes used for the infusion of anesthetics, for example, for pain relief during childbirth. Arteries and veins are associated with the spinal nerves and nerve roots. Some segmental arteries provide crucial anastomotic channels for blood flow from the aorta to augment flow from the anterior and posterior spinal arterial systems, which cannot sustain the entire spinal cord; surgical procedures affecting blood flow through the aorta may affect the spinal cord. The sympathetic chain ganglia (paravertebral), important for fight-or-flight responses, lie adjacent to the vertebral body ventrally. The dorsal and ventral rami of the spinal nerves provide innervation to specific regions. The spinous process of the vertebral body extends dorsally, where it can be palpated by physical exam. **B,** The

subarachnoid space of a lumbar vertebra, containing the filum terminale and roots of the cauda equina.

**CLINICAL POINT**

The dorsal and ventral roots travel through the adjacent subarachnoid space and join to form the peripheral nerves. These nerve roots and resultant nerves are sometimes the targets of acute, autoimmune, inflammatory demyelinating conditions (polyradiculoneuropathy), called Guillain-Barré syndrome (GBS). GBS is an acute, progressive, symmetrical weakness that usually progresses from distal to proximal in the limbs and may result in total paralysis of all musculature, including respiratory musculature, occurring over the course of hours to days. The weakness is often accompanied by paresthesias in the distal extremities. GBS is commonly preceded by an infectious process, such as *Campylobacter jejuni* enteritis, Epstein-Barr syndrome, or cytomegaloviral infections, or by *Mycoplasma pneumoniae*, which presumably triggers the autoimmune attack on peripheral myelin. Most patients with GBS recover through a remyelinating process, which may take a year or more, although at least 10% are left with severe deficits, and a small percent of individuals die.



**A. Sections through spinal cord at various levels****B. Principal fiber tracts of spinal cord (composite)****5.6 SPINAL CORD: WHITE AND GRAY MATTER**

**A,** Seven representative spinal cord levels. The images depict their relative sizes and the variability in the amount of gray matter at each level. Levels associated with the limbs have greater amounts of gray matter. White matter increases in absolute amount from caudal to rostral, reflecting the level-by-level addition of ascending tracts and the termination of descending tracts. **B,** The gray matter consists of dorsal and ventral horns, and in the T1–L2 segments, there is an intermediolateral cell column (lateral horn) where preganglionic sympathetic neurons reside. The white matter is subdivided into dorsal, lateral, and ventral funiculi, each containing multiple tracts (fasciculi, bundles). The tracts conveying pain and temperature information rostrally travel in the anterolateral funiculus, the spinothalamic/spinoreticular system. Fine discriminative sensation is conveyed through the dorsal funiculus. The major descending upper motor neuronal tract, the corticospinal tract, travels mainly in the lateral funiculus, with a component present in the medial part of the anterior funiculus. Dorsal root entry zones and ventral root exit zones are present at each cross-sectional level.

**CLINICAL POINT**

The spinal cord levels show considerable variation in the size of the dorsal and ventral horns. The cervical and lumbosacral enlargements

reflect the large number of sensory, intermediate, and motor neurons necessary for the afferent and efferent innervation of the limbs. The lower motor neurons (LMNs) in these enlargements are particularly vulnerable to poliovirus. Acute poliomyelitis results in the death of some LMNs, with resultant denervation of corresponding muscles, atrophy, flaccid paralysis, and loss of tone and reflexes. Remaining LMNs that survive the viral infection may sprout axons to reoccupy the sites on skeletal muscles left denuded by death of their original LMNs. These remaining LMNs then possess larger motor units (innervate more muscle fibers per cell body); this extra burden may account for some of the later degeneration and weakness seen in postpolio syndrome many decades after the acute disease. Polio is unusual in the United States and Western countries because of widespread vaccination programs, but still occurs in some developing nations.

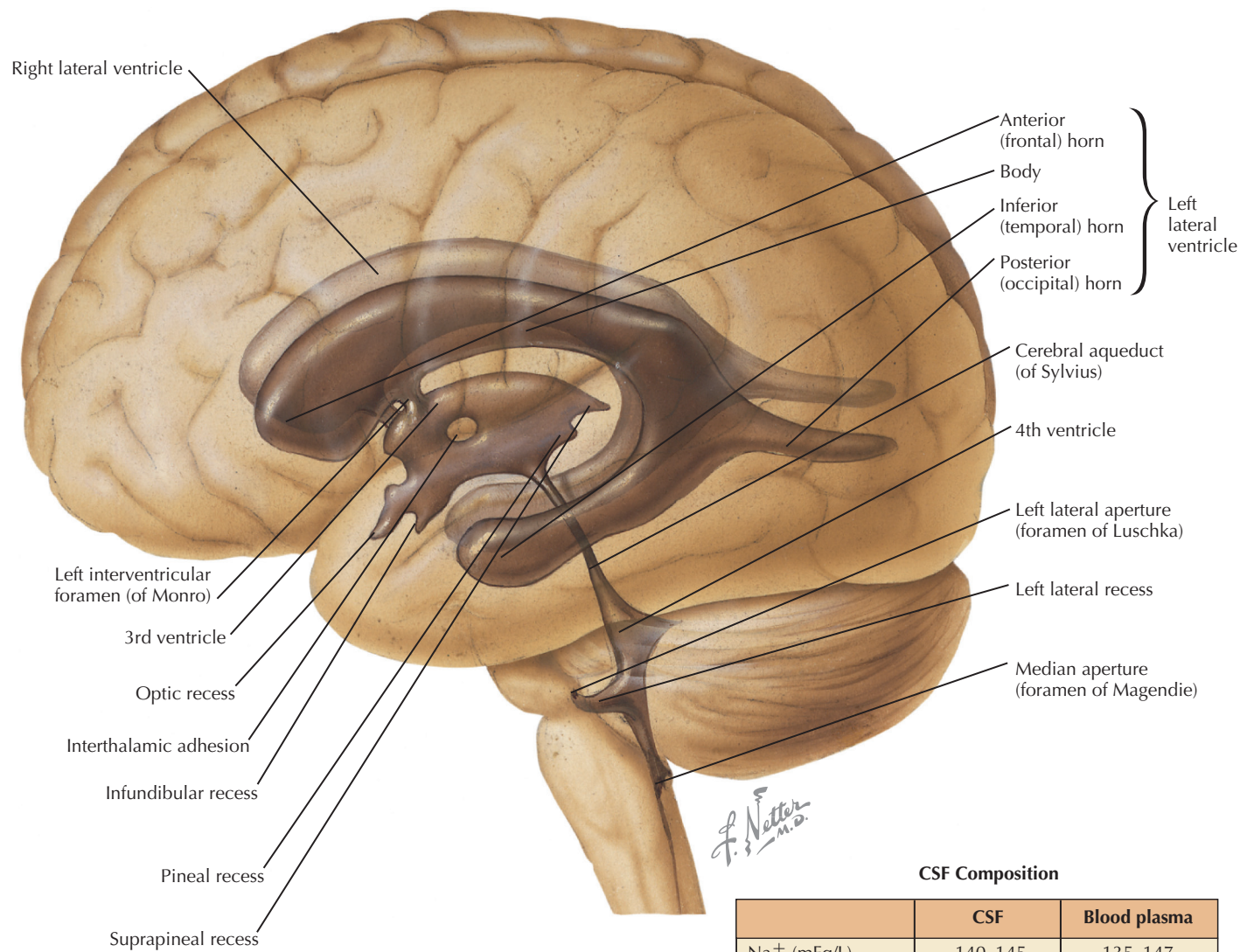
The ascending and descending tracts are clustered in specific zones of the dorsal (posterior), lateral, and ventral (anterior) funiculi. Some regions of these funiculi are selectively vulnerable to vitamin B<sub>12</sub> (cobalamin) deficiency; impairment of methylmalonyl-CoA mutase results in damage to myelinated fibers. Pernicious anemia may precede neurological symptoms by months or years. Damage involves the dorsal funiculi and components of the lateral funiculi. Dorsal column damage is accompanied by paresthesias of the feet and legs and often of the hands and arms, with sensory ataxia and broad-based gait; by loss of vibratory sensation, joint position sense, and fine discriminatory touch; and by Romberg's sign. Lateral funiculus damage is accompanied by spastic paraparesis with increased tone and muscle stretch reflexes and plantar extensor responses. Early recognition of this condition and treatment with B<sub>12</sub> can lead to rapid reversal and recovery.

# 6

## VENTRICLES AND THE CEREBROSPINAL FLUID

- 6.1 Ventricular Anatomy
- 6.2 Ventricular Anatomy in Coronal Forebrain Section
- 6.3 Anatomy of the Fourth Ventricle: Posterior View with Cerebellum Removed
- 6.4 Anatomy of the Fourth Ventricle: Lateral View
- 6.5 Magnetic Resonance Imaging of the Ventricles: Axial and Coronal Views
- 6.6 Circulation of the Cerebrospinal Fluid

Ventricles of Brain



CSF Composition

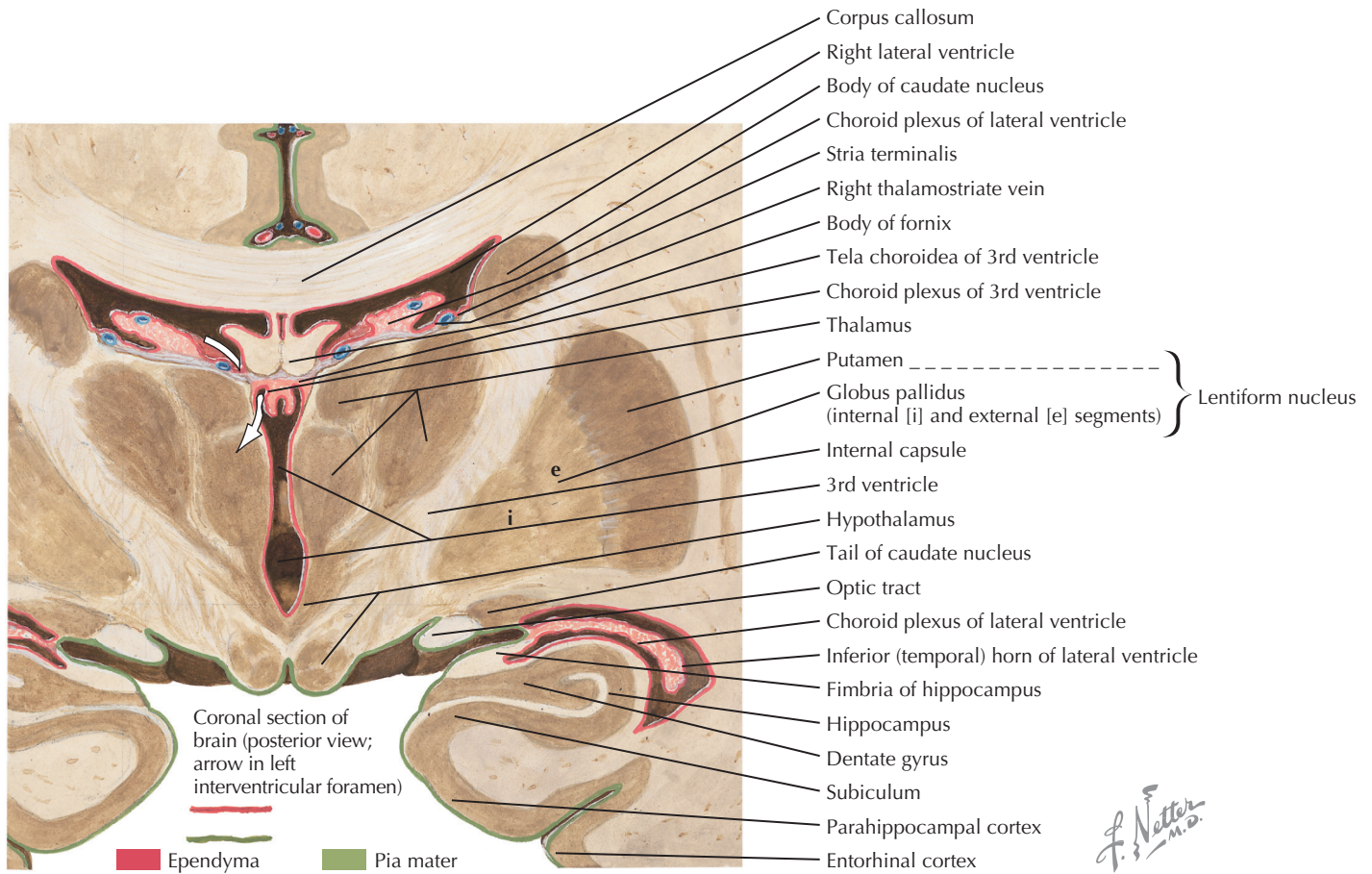
	CSF	Blood plasma
Na <sup>+</sup> (mEq/L)	140–145	135–147
K <sup>+</sup> (mEq/L)	3	3.5–5.0
Cl <sup>−</sup> (mEq/L)	115–120	95–105
HCO <sub>3</sub> <sup>−</sup> (mEq/L)	20	22–28
Glucose (mg/dL)	50–75	70–110
Protein (g/dL)	0.05–0.07	6.0–7.8
pH	7.3	7.35–7.45

6.1 VENTRICULAR ANATOMY

The lateral ventricles are C-shaped, reflecting their association with the developing telencephalon as it sweeps upward, back, and then down and forward as the temporal lobe. The position of the lateral ventricles in relation to the head and body of the caudate nucleus is an important radiological landmark in a variety of conditions, such as hydrocephalus, caudate atrophy in Huntington’s disease, and shifting of the midline with a tumor. Cerebrospinal fluid (CSF) flows through the interventricular foramen of Monro into the narrow third ven-

tricle, then into the cerebral aqueduct and the fourth ventricle. Blockage of flow in the aqueduct can precipitate internal hydrocephalus, with swelling of the ventricles rostral to the site of blockage. The escape sites where CSF can flow into expanded regions of the subarachnoid space called cisterns are the medial foramen of Magendie and the lateral foramina of Luschka. These foramina are additional sites where blockage of CSF flow can occur. The choroid plexus, extending into the ventricles, produces the CSF. See Videos 6-1 and 6-2.

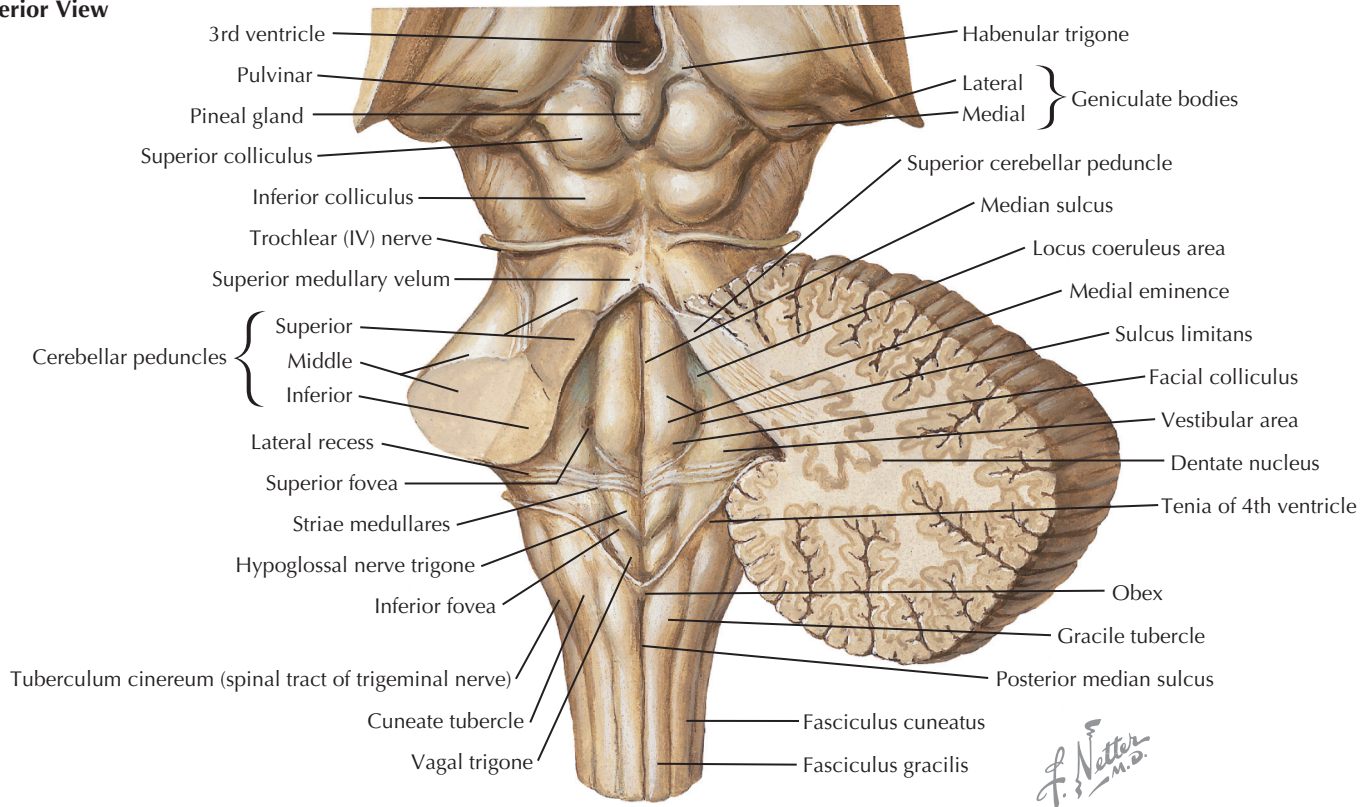




## 6.2 VENTRICULAR ANATOMY IN CORONAL FOREBRAIN SECTION

A coronal section through the diencephalon shows the bodies of the lateral ventricles, the narrow interventricular foramina of Munro, and the midline third ventricle. The flow of CSF is

from the lateral ventricles into the third ventricle. The choroid plexus protrudes into both the lateral and third ventricles and produces CSF. The temporal (inferior) pole of the lateral ventricle and its associated choroid plexus is shown in the temporal lobe.

**Posterior View**

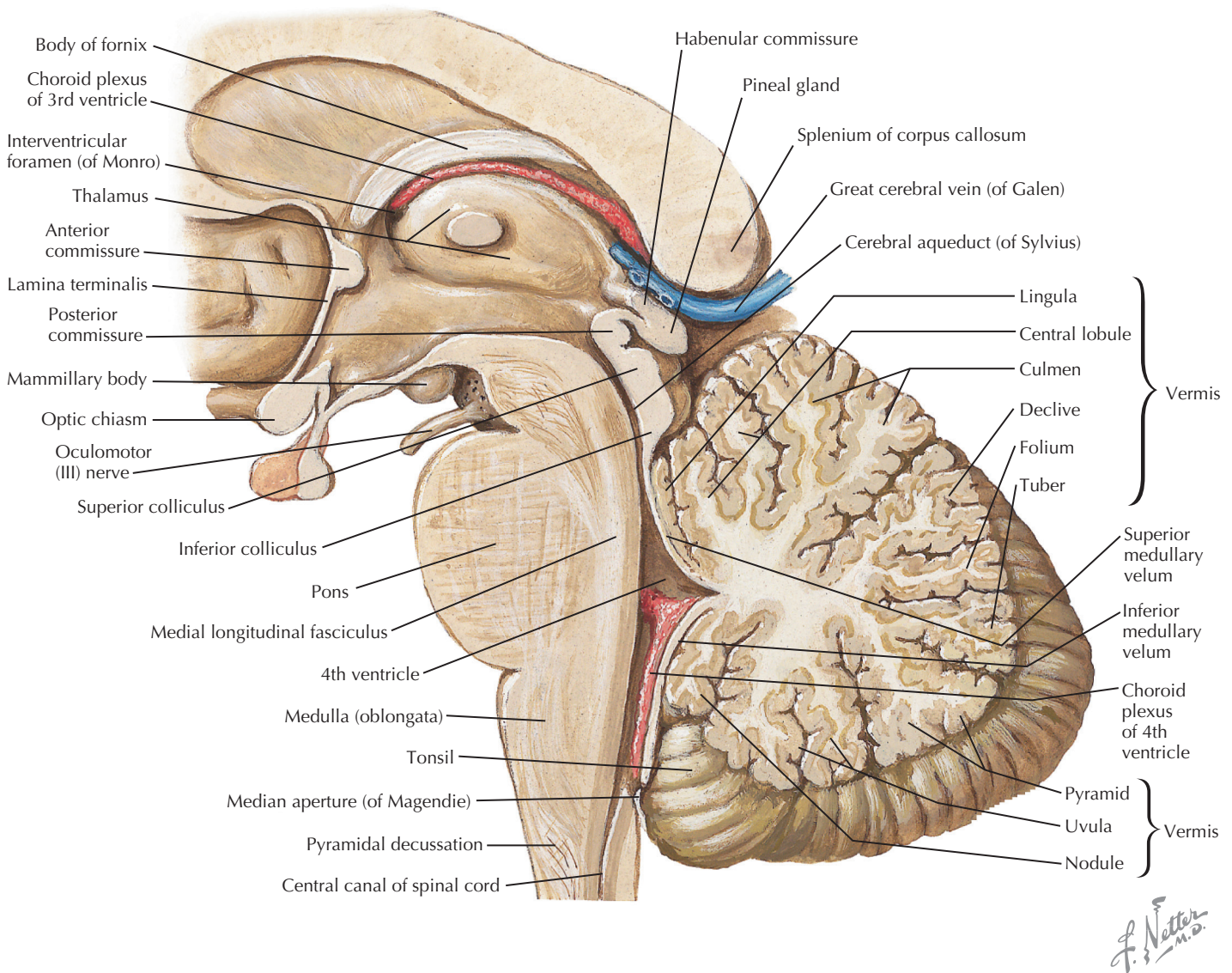
### 6.3 ANATOMY OF THE FOURTH VENTRICLE: POSTERIOR VIEW WITH CEREBELLUM REMOVED

The rhomboid-shaped fourth ventricle extends through the pons and medulla. The foramina of Magendie and Luschka must remain patent for proper flow of the CSF into the cisterns. Bilaterally symmetrical protrusions, depressions, and sulci on the floor of the fourth ventricle define the underlying anatomy of brain stem regions, such as the hypoglossal, vagal,

and vestibular areas. Vital brain stem centers for cardiovascular, respiratory, and metabolic functions just below the floor of the fourth ventricle can be damaged by tumors in the region. The lateral margins of the fourth ventricle are embraced by the huge cerebellar peduncles interconnecting the cerebellum with the brain stem and diencephalon. These anatomical relationships are important when interpreting imaging studies in the compact brain stem regions where the diagnosis of tumors and vascular lesions is challenging.



### Median Sagittal Section



### 6.4 ANATOMY OF THE FOURTH VENTRICLE: LATERAL VIEW

In a midsagittal section, the rhomboid shape of the fourth ventricle is shown. Rostrally, the narrow cerebral aqueduct leads into the fourth ventricle; caudally, the foramen of Magendie provides for escape of CSF into a cistern of the subarachnoid space. CSF normally does not flow through the central canal of the spinal cord. The dorsal surface of the brain stem is on the floor of the fourth ventricle; the cerebral peduncles form the lateral boundaries; and the medullary velum and cerebellum form the roof of the fourth ventricle. The choroid plexus is present in the fourth ventricle. In the diencephalon, the shallow depression of the third ventricle and the interventricular foramen of Munro are shown.

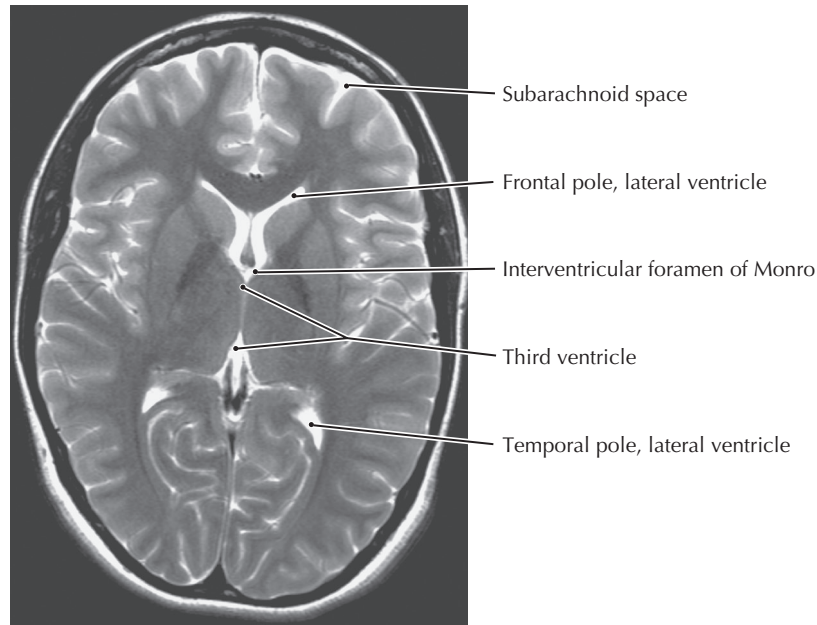
#### CLINICAL POINT

The choroid plexus is the site of production of CSF in the lateral, third, and fourth ventricles. Even subtle changes in equilibrium between CSF production and absorption can result in altered intraventricular

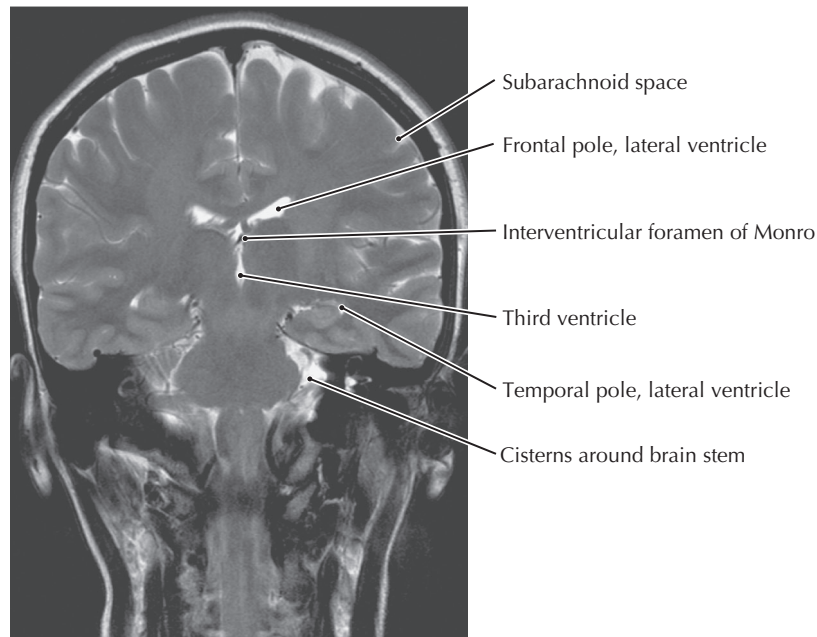
pressure and intracranial pressure. Hydrocephalus is most commonly caused by obstruction of outflow (internal hydrocephalus) or failure of appropriate absorption into the venous sinuses (external hydrocephalus). Occasionally, alterations in CSF production by the choroid plexus may occur. Inflammation of the choroid plexus or a papilloma can lead to hypersecretion hydrocephalus. In contrast, damage to the choroid plexus by radiation, trauma, or meningitis or secondary to lumbar puncture may result in diminished CSF production (hypoli-quorrhea), with resultant long-lasting and persistent headache that is responsive to change in posture.

The CSF escapes from the ventricular system from the medial foramen of Magendie and the lateral foramina of Luschka of the fourth ventricle. These apertures must remain unobstructed in order to allow CSF to escape into the subarachnoid space, bathe the CNS, and then be absorbed into the venous sinuses through the arachnoid granulations. The foramen of Magendie is the most important of these apertures; it may become obstructed by tonsillar herniation into the foramen magnum as the result of Arnold-Chiari malformation; by a cerebellar tumor; or by an intraventricular tumor that obstructs the lower portion of the fourth ventricle. Such an obstruction at this lower level results in expansion of the entire ventricular system, including the fourth, third, and lateral ventricles.





**A. Axial view**

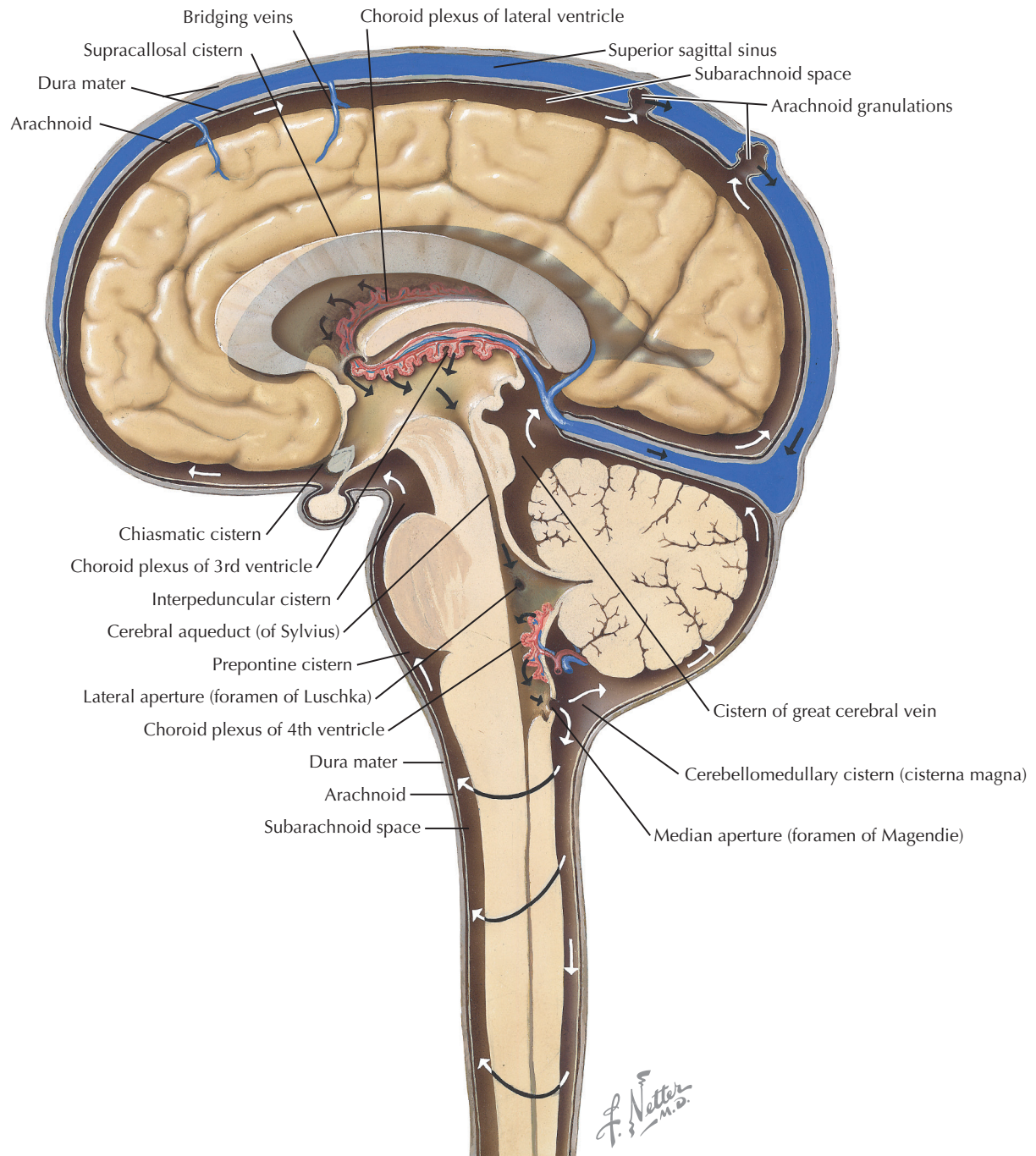


**B. Coronal view**

### 6.5 MAGNETIC RESONANCE IMAGING OF THE VENTRICLES: AXIAL AND CORONAL VIEWS

A and B, These T2-weighted magnetic resonance images of the brain in axial and coronal sections demonstrate major components of the ventricular system (in white) and some

cisternal structures. Both the frontal and temporal poles of the lateral ventricles are visible. Figure 3.11 also illustrates a T2-weighted midsagittal image, revealing the midsagittal ventricular system and related cisterns.



## 6.6 CIRCULATION OF THE CEREBROSPINAL FLUID

CSF flows internally through the ventricles, from lateral ventricles to the third ventricle to the cerebral aqueduct to the fourth ventricle. The CSF passes through several points where blockage or obstruction could precipitate internal hydrocephalus and increased intracranial pressure. CSF flow from the fourth ventricle into the cisterns of the subarachnoid space, surrounding the brain and spinal cord, provides the external protective cushioning and buoyancy to protect underlying central nervous system tissue from minor trauma. Some cisterns such as the lumbar cistern provide sites for withdrawal

of CSF (lumbar puncture). The CSF is absorbed from the subarachnoid space into the venous drainage through the arachnoid granulations by a process driven by the pressure of flow through these one-way valves. Disruption of this drainage results in external hydrocephalus. Thus, production, flow, and absorption of CSF must be in precise balance. The flow of the CSF in the ventricles also can act as a fluid-delivery system for downstream influences of specific mediators (e.g., prostaglandins, interleukins) and represents an internal paracrine communication channel for some structures close to the ventricles.

# 7

## VASCULATURE

### Arterial System

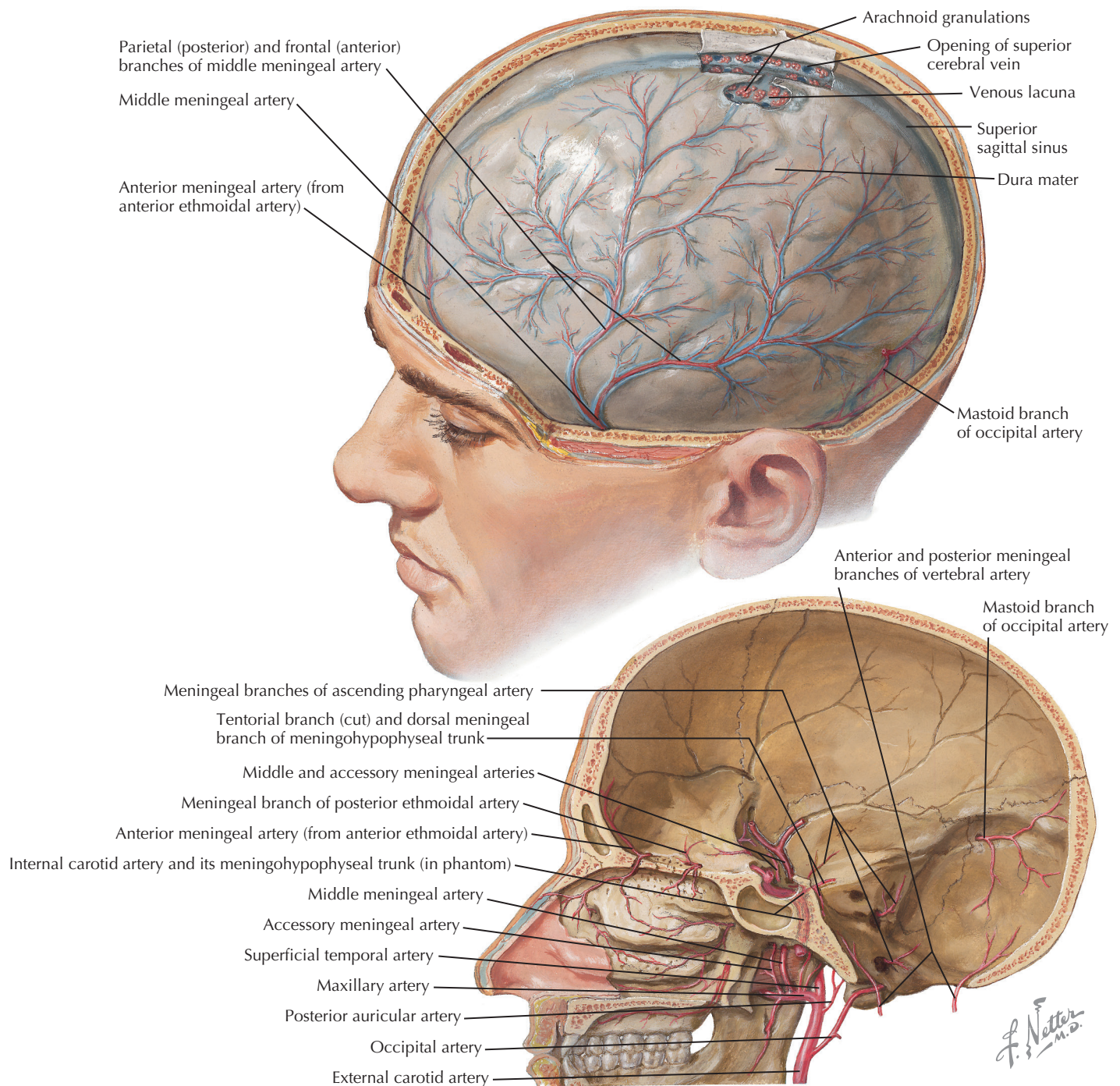
- 7.1 Meningeal Arteries: Relationship to Skull and Dura
- 7.2 Arterial Supply to the Brain and Meninges
- 7.3 Common Sites of Cerebrovascular Occlusive Disease
- 7.4 Internal Carotid and Ophthalmic Artery Course
- 7.5 Arterial Distribution to the Brain: Basal View
- 7.6 Arterial Distribution to the Brain: Cutaway Basal View Showing the Circle of Willis
- 7.7 Arterial Distribution to the Brain: Frontal View with Hemispheres Retracted
- 7.8 Arterial Distribution to the Brain: Coronal Forebrain Section
- 7.9 Types of Strokes
- 7.10 Schematic of Arteries to the Brain
- 7.11 Circle of Willis: Schematic Illustration and Vessels in Situ
- 7.12 Arterial Distribution to the Brain: Lateral and Medial Views
- 7.13 Territories of the Cerebral Arteries
- 7.14 Magnetic Resonance Angiography: Frontal and Lateral Views
- 7.15 Angiographic Anatomy of the Internal Carotid Circulation
- 7.16 Vertebrobasilar Arterial System

- 7.17 Angiographic Anatomy of the Vertebrobasilar System
- 7.18 Occlusive Sites of the Vertebrobasilar System
- 7.19 Vascular Supply to the Hypothalamus and the Pituitary Gland
- 7.20 Arterial Blood Supply to the Spinal Cord: Longitudinal View
- 7.21 Anterior and Posterior Spinal Arteries and Their Distribution
- 7.22 Arterial Supply to the Spinal Cord: Cross-Sectional View

### Venous System

- 7.23 Meninges and Superficial Cerebral Veins
- 7.24 Veins: Superficial Cerebral, Meningeal, Diploic, and Emissary
- 7.25 Venous Sinuses
- 7.26 Deep Venous Drainage of the Brain
- 7.27 Deep Venous Drainage of the Brain: Relationship to the Ventricles
- 7.28 Carotid Venograms: Venous Phase
- 7.29 Magnetic Resonance Venography: Coronal and Sagittal Views
- 7.30 Venous Drainage of the Brain Stem and the Cerebellum
- 7.31 Venous Drainage of the Spinal Cord



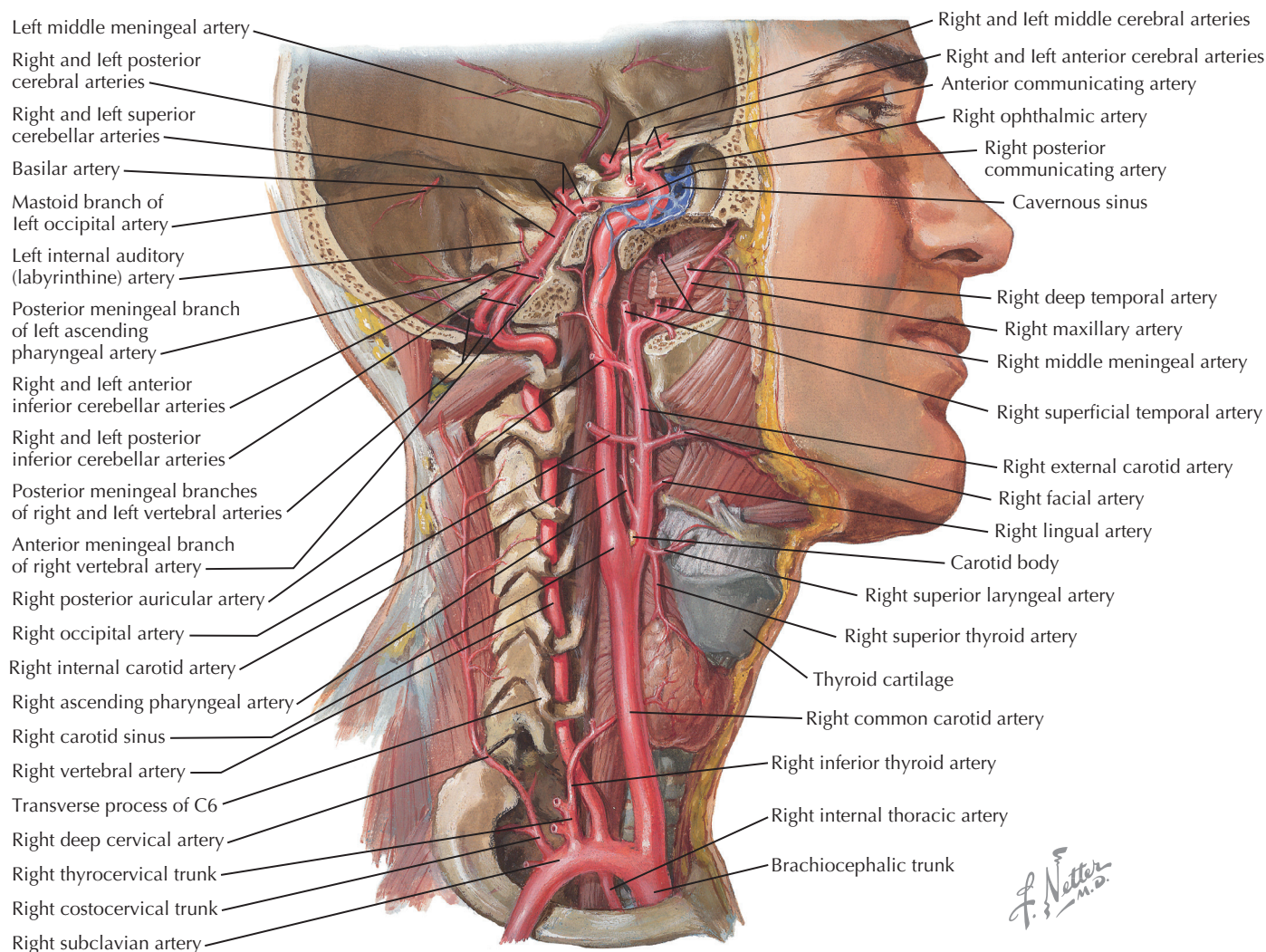


## ARTERIAL SYSTEM

### 7.1 MENINGEAL ARTERIES: RELATIONSHIP TO SKULL AND DURA

Meningeal arteries are found in the outer portion of the dura; they supply it with blood. They also help to supply blood to adjacent skull and have some anastomoses with cerebral arteries. The skull has grooves, or sulci, for the meningeal vessels. This relationship reflects an important functional conse-

quence of skull fractures. Fractures can rip a meningeal artery (usually the middle meningeal artery) and allow arterial blood to accumulate above the dura. Such an epidural hematoma is a space-occupying mass and can produce increased intracranial pressure and risk for herniation of the brain, particularly across the free edge of the tentorium cerebelli. Even very fine fractures can have this dangerous consequence.



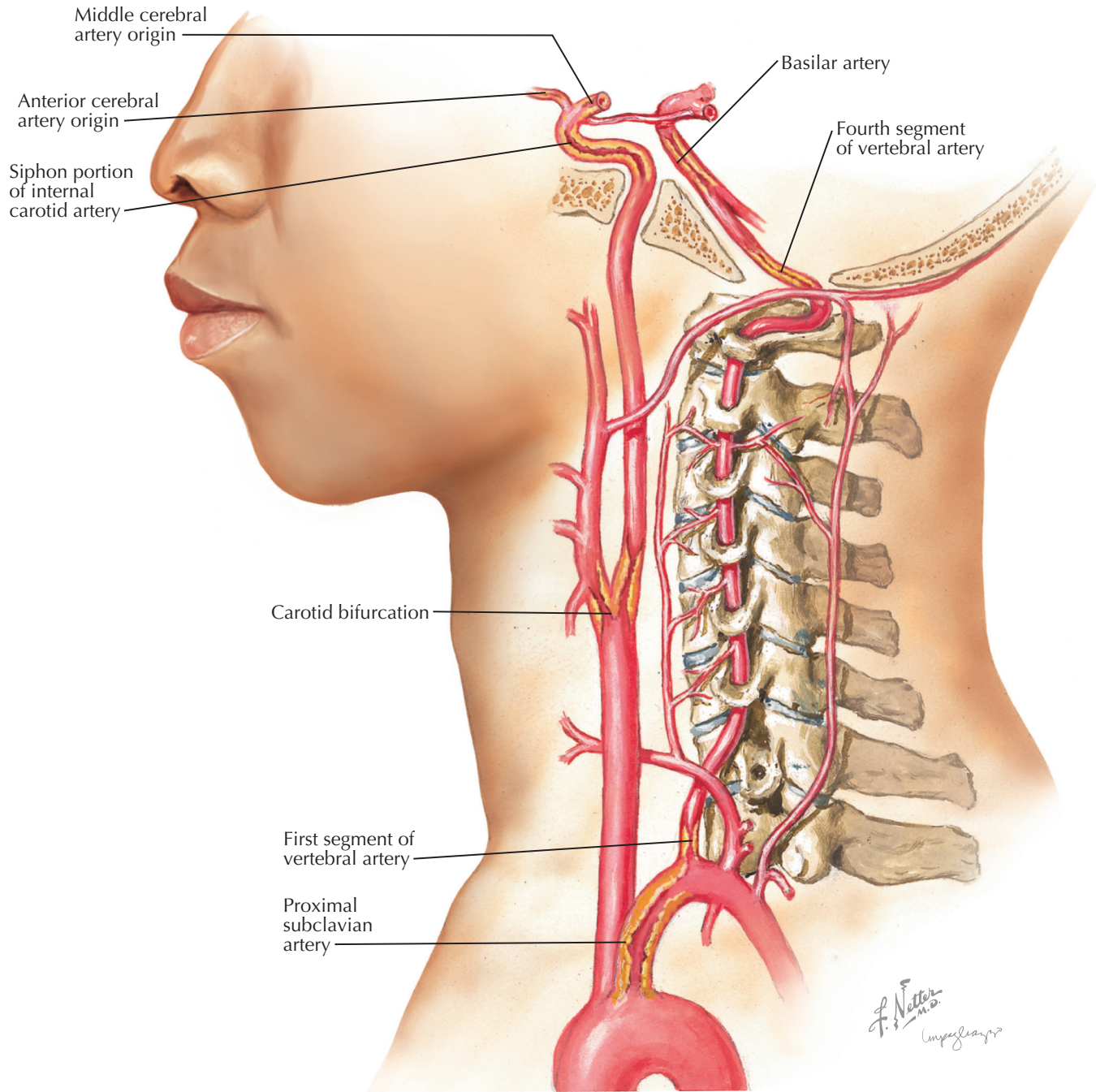
## 7.2 ARTERIAL SUPPLY TO THE BRAIN AND MENINGES

The internal carotid artery (ICA) and the vertebral artery ascend through the neck and enter the skull to supply the brain with blood. The tortuous bends and sites of branching (such as the bifurcation of the common carotid artery into the internal and external carotids) produce turbulence of blood flow and are sites where atherosclerosis can occur. The bifurcation of the common carotid is particularly vulnerable to plaque formation and occlusion, threatening the major anterior part of the brain with ischemia, which would result in a stroke. The ICA passes through the cavernous sinus, a site where carotid-cavernous fistulae can occur, resulting in damage to the extraocular and trigeminal cranial nerves, which also pass through this sinus. Studies of blood flow through these arteries are important diagnostic tools. Magnetic resonance arteriography and Doppler flow studies have, for most purposes, replaced the older dye studies for performing cerebral angiography.

### CLINICAL POINT

The paired carotid arteries and vertebral arteries supply the brain and part of the spinal cord with blood. The carotids supply the anterior circulation, including most of the forebrain except for the occipital lobe and inferior surface of the temporal lobe. The bifurcation of the common carotid artery is a common site of plaque formation in atherosclerosis, leading to gradual occlusion of blood flow to the forebrain on the ipsilateral side. Early warnings can be seen in the form of transient ischemic attacks, forerunners of a full-blown stroke. The best treatment is prevention, with exercise, proper diet and weight control, careful regulation of lipid levels and other contributing factors such as inflammatory mediators. In cases in which severe and symptomatic occlusion has occurred as the result of atherosclerotic plaque, carotid endarterectomy can be performed to remove the plaque and attempt to open up more robust flow to the anterior circulation. Carefully performed controlled studies have established criteria that determine which patients can best benefit from this surgical procedure as opposed to more conservative medical treatment. Current studies are investigating the use of carotid stents to enhance blood flow to the brain.





### 7.3 COMMON SITES OF CEREBROVASCULAR OCCLUSIVE DISEASE

Atherosclerosis is the most common cause of internal carotid disease, accounting for many cerebral ischemic events, particularly in the elderly. Atherosclerotic plaques are formed by deposition of circulating lipids and the accumulation of fibrous tissue in the subintimal layer of large and medium arteries, exacerbated by the presence of inflammatory mediators and shearing forces from hypertension. Plaque formation particularly occurs at arterial branch points, where turbulence is maximal.

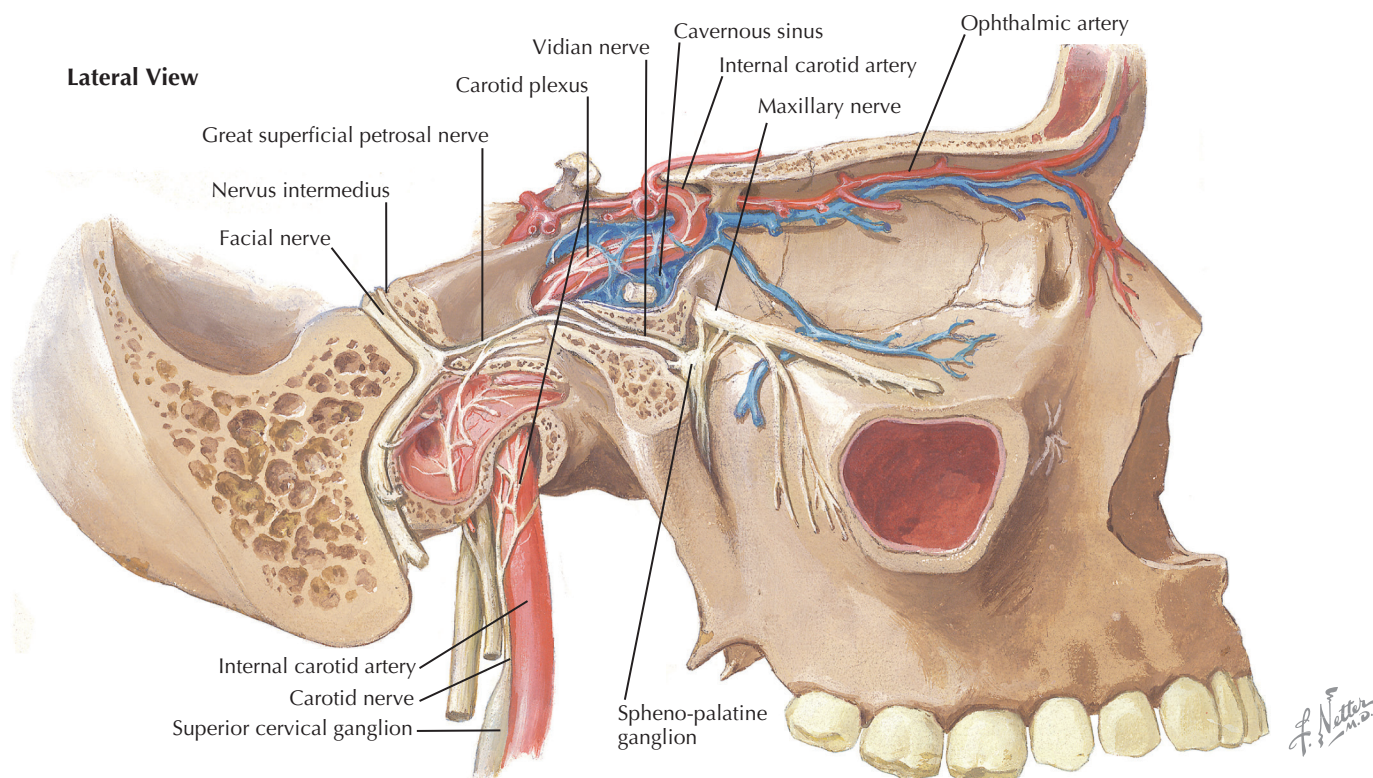
Disruption of the endothelial surface can result in thrombus formation, platelet aggregation, and production of emboli,

which are carried upstream into end branches of the vascular system.

In addition to genetic factors, predisposing risks for atherosclerotic plaque formation include smoking, type II diabetes, hypertension, and hypercholesterolemia.

Illustrated here are the most common sites for atherosclerosis in the cerebral circulation, including the bifurcation of the common carotid artery and origin of the internal carotid artery, carotid siphon, main stems of the middle and anterior cerebral arteries, proximal subclavian artery, first segment of the vertebral artery, fourth segment of the vertebral artery, and basilar artery.

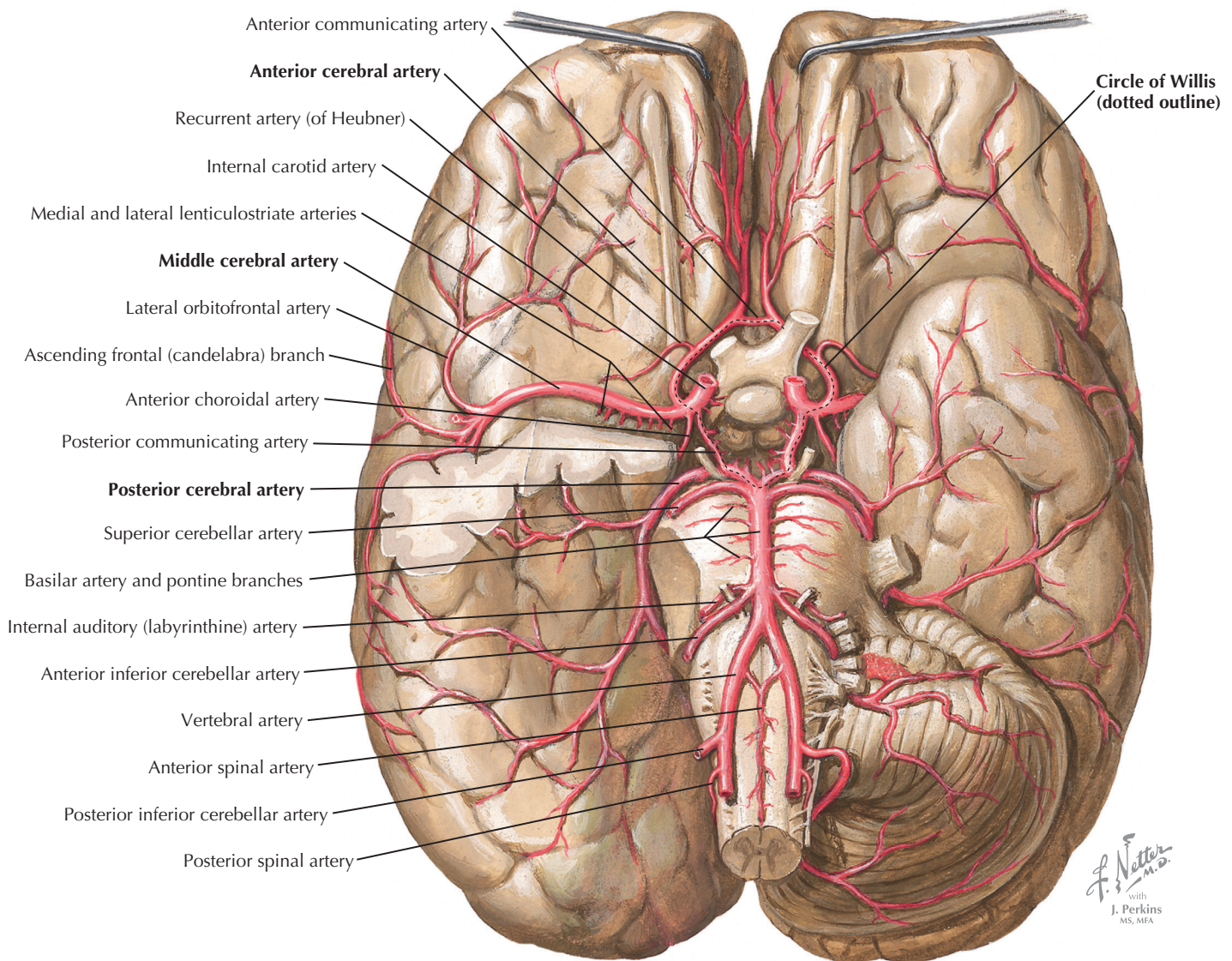




#### 7.4 INTERNAL CAROTID AND OPHTHALMIC ARTERY COURSE

The ophthalmic artery is the first major branch of the internal carotid artery (ICA). It supplies the eyeball, ocular muscles, and adjacent structures with blood. This artery is commonly involved in the first phases of clinical recognition of cerebro-

vascular disease. Because of its position as the first branch of the ICA, emboli from atherosclerotic plaques that are found at sites such as the bifurcation of the common carotid artery may travel through the ophthalmic artery, resulting in a transient ischemic attack with the symptom of fleeting blindness (amaurosis fugax) in the affected eye.



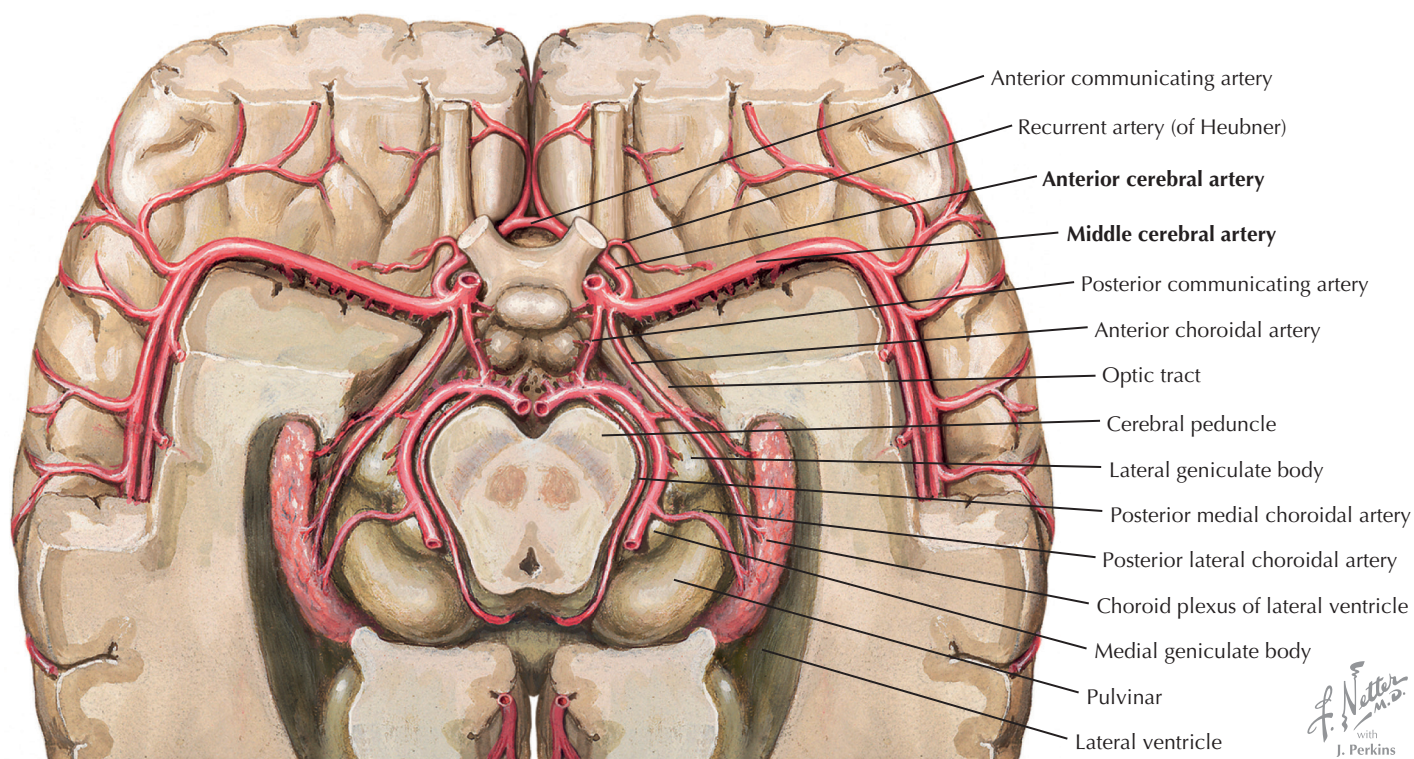
## 7.5 ARTERIAL DISTRIBUTION TO THE BRAIN: BASAL VIEW

The anterior circulation (middle and anterior cerebral arteries; MCAs, ACAs) and the posterior circulation (the verteobasilar system and its end branch, the posterior cerebral artery; PCA) and their major branches are shown. The right temporal pole is removed to show the course of the MCA through the lateral fissure. The circle of Willis (the paired ACAs, MCAs, and PCAs and the anterior and two posterior communicating arteries) surrounds the basal hypothalamic area. The circle of Willis appears to allow free flow of blood around the anterior and posterior circulation of both sides, but usually it is not sufficiently patent to allow bypass of an occluded zone. See [Video 7-1](#).

### CLINICAL POINT

The verteobasilar system supplies blood to the posterior circulation of the brain, including most of the brain stem, part of the diencephalon, and the occipital and inferior temporal lobes of the forebrain. The paired PCAs are the end arteries of the verteobasilar system. An infarct in the PCAs (top of the basilar infarct) results in damage to the ipsilateral occipital lobe, including both the upper and lower banks of the calcarine fissure. Functionally, this infarct affecting one side results in contralateral blindness, called contralateral homonymous hemianopia. There may be macular sparing if the MCA has some anastomoses with the posterior cerebral circulation.





## 7.6 ARTERIAL DISTRIBUTION TO THE BRAIN: CUTAWAY BASAL VIEW SHOWING THE CIRCLE OF WILLIS

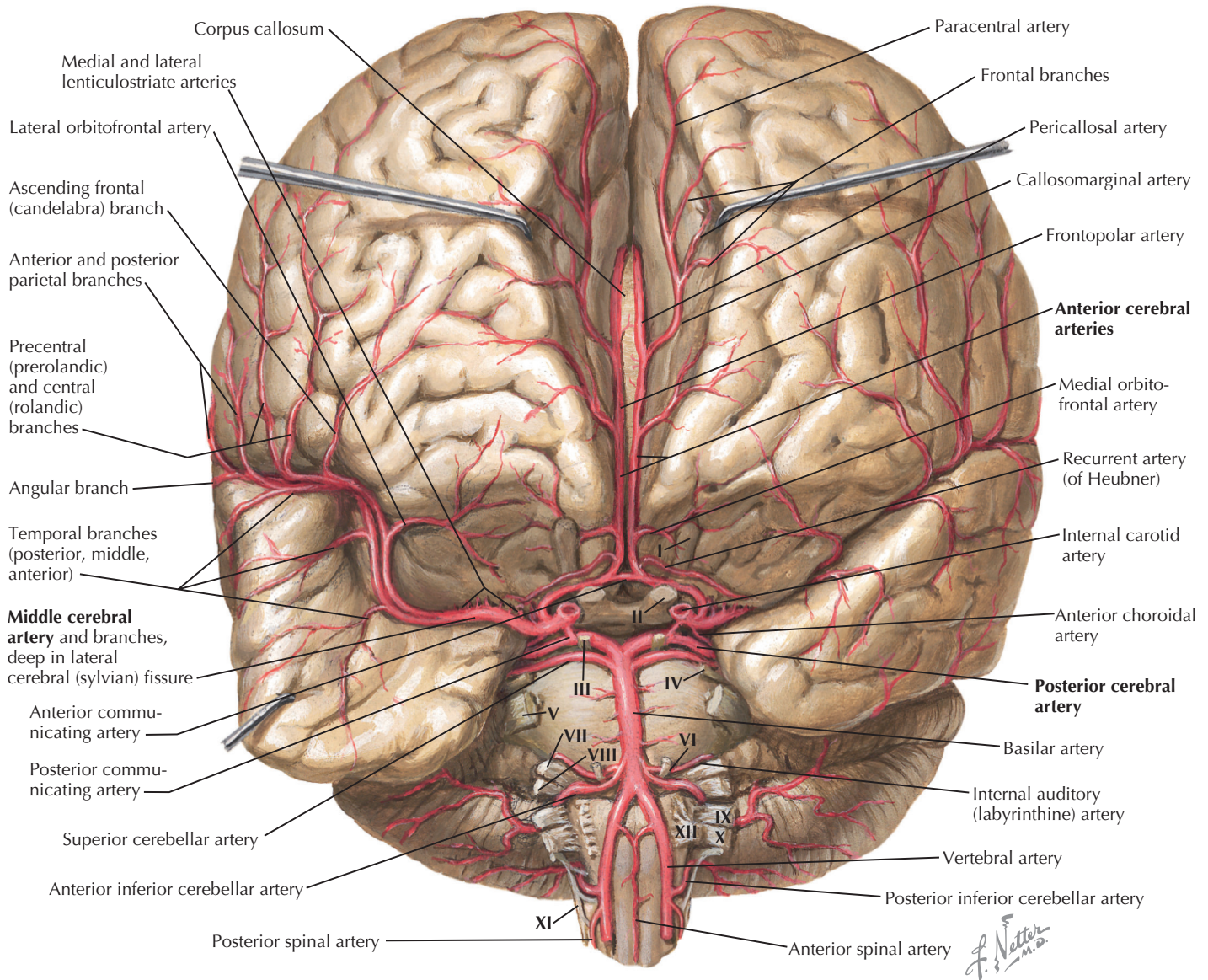
The circle of Willis and the course of the choroidal arteries are shown. The arteries supplying the brain are end arteries and do not have sufficient anastomotic channels with other arteries to sustain blood flow in the face of disruption. The occlusion of an artery supplying a specific territory of the brain results in functional damage that affects the performance of structures deprived of adequate blood flow. See [Video 7-2](#).

### CLINICAL POINT

Obstruction of the MCA near its origin is relatively unusual compared with obstruction or infarcts in selected branches, but it demonstrates the full range of blood supply of this critical artery. Obstruction near the origin usually results from embolization, not from atherosclerotic or thrombotic lesions. It causes contralateral hemiplegia (resolving to spastic), contralateral central facial palsy (lower face), contralateral hemianesthesia, contralateral homonymous hemianopia, and global aphasia if the left hemisphere is involved. Additional problems with anosognosia (inability to recognize a physical disability), contralateral neglect, and spatial disorientation may occur.



## Frontal View with Hemispheres Retracted, Tilted for a View of the Ventral Brain Stem



## 7.7 ARTERIAL DISTRIBUTION TO THE BRAIN: FRONTAL VIEW WITH HEMISPHERES RETRACTED

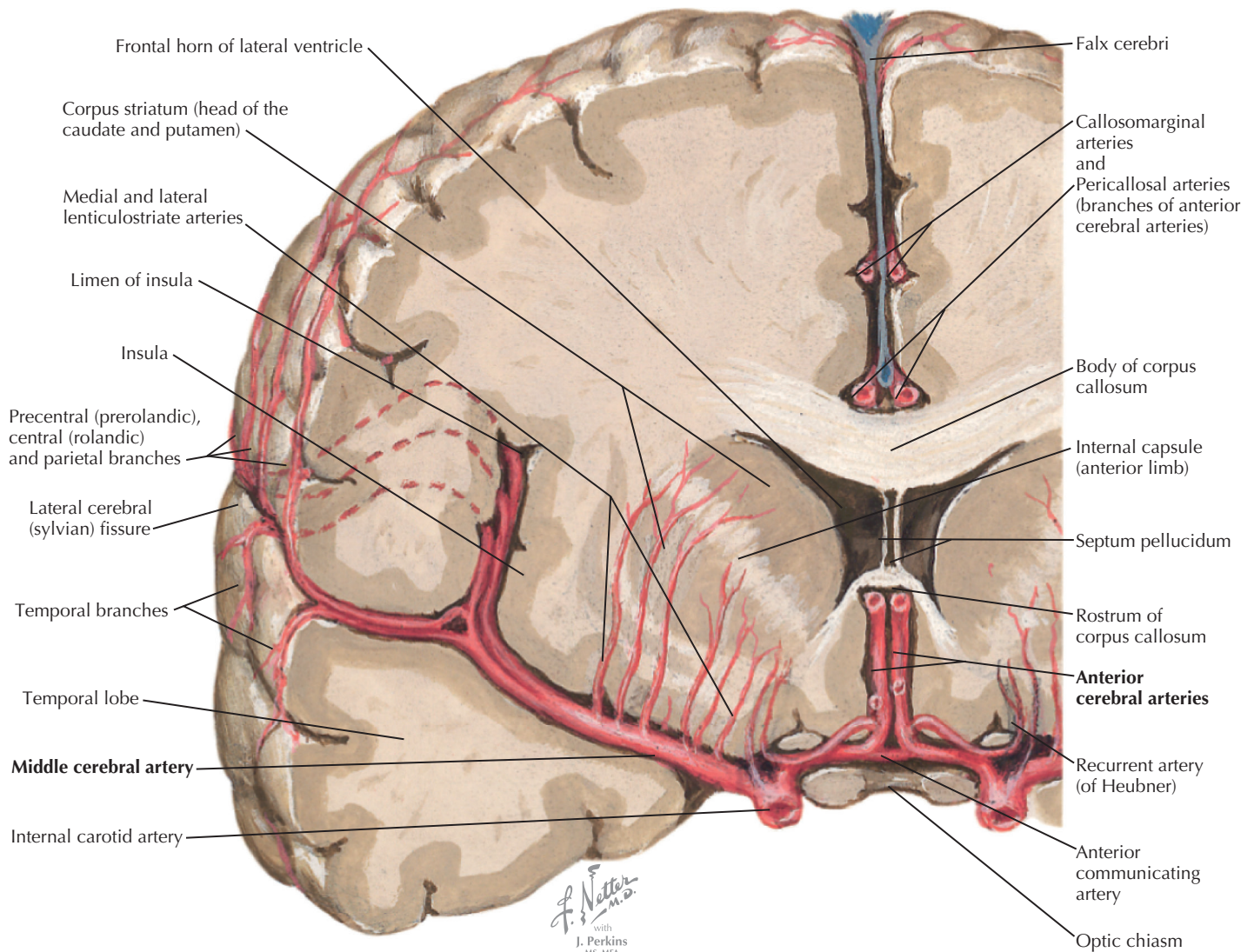
With the hemispheres retracted, the course of the ACAs and their distribution along the midline are visible. This artery supplies blood to the medial zones of the sensory and motor cortex, which are associated with the contralateral lower extremity; an ACA stroke thus affects the contralateral lower limb. With the lateral fissure opened up, the MCA is seen to course laterally and to give branches to the entire convexity of the hemisphere. End-branch infarcts of the MCA affect the contralateral upper extremity and, if on the left, also affect language function. More proximal MCA infarcts affecting the MCA distribution to the internal capsule can cause full contralateral hemiplegia with drooping of the contralateral lower face; this results from damage to corticospinal and other corticomotor fibers traveling in the posterior limb of the internal

capsule and damage to corticobulbar fibers traveling in the genu of the internal capsule.

### CLINICAL POINT

The ACA branches from the internal carotid as it splits from the middle cerebral artery. It supplies a medial strip of the forebrain with blood. ACA occlusion is usually caused by embolization, although an anterior communicating artery aneurysm, vasospasm resulting from a subarachnoid hemorrhage, or subfalcine herniation can occlude this artery. If the ACA is occluded distal to the recurrent artery of Heubner, it results in contralateral spastic paresis and sensory loss in the lower extremity. A more proximal lesion involving the recurrent artery of Heubner may involve the upper body and limb as well. In addition, there may be internal sphincter weakness of the urinary bladder, frontal release signs, and conjugate deviation of the eyes toward the side of the lesion (damage to frontal eye fields with unopposed deviation from the intact side).

## Coronal Section through the Head of the Caudate Nucleus

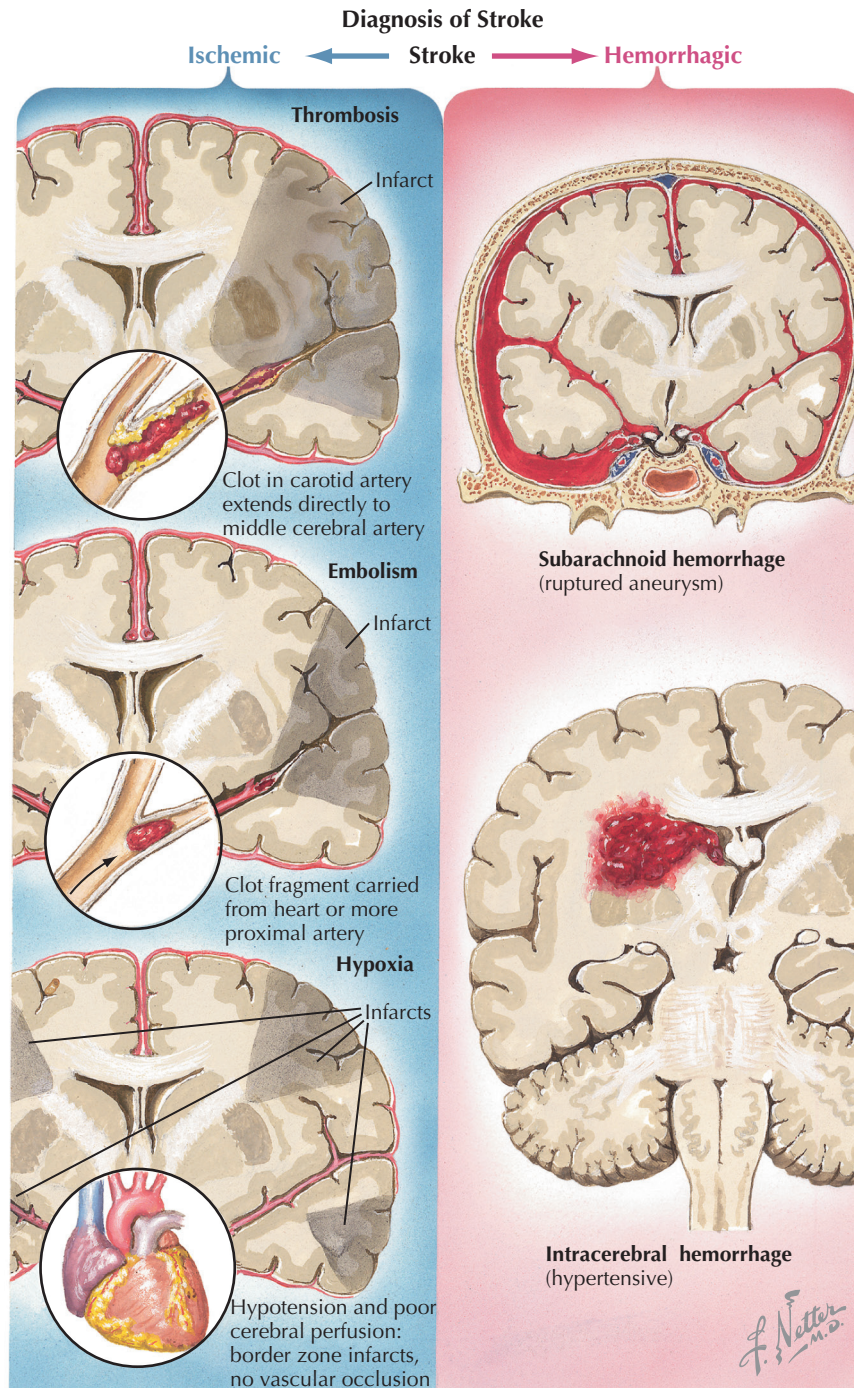


## 7.8 ARTERIAL DISTRIBUTION TO THE BRAIN: CORONAL FOREBRAIN SECTION

The MCA is the major continuation of the internal carotid artery (ICA). The MCA travels through the lateral fissure, supplying branches both to deep structures and to the convexity of the cerebral cortex. The lenticulostriate arteries, some-

times called the arteries of stroke, are thin branches of the MCA that penetrate into the basal ganglia and internal capsule regions of the forebrain. A stroke in this territory produces a classic contralateral hemiplegia (spastic) with aphasia, often worse in the upper extremity.



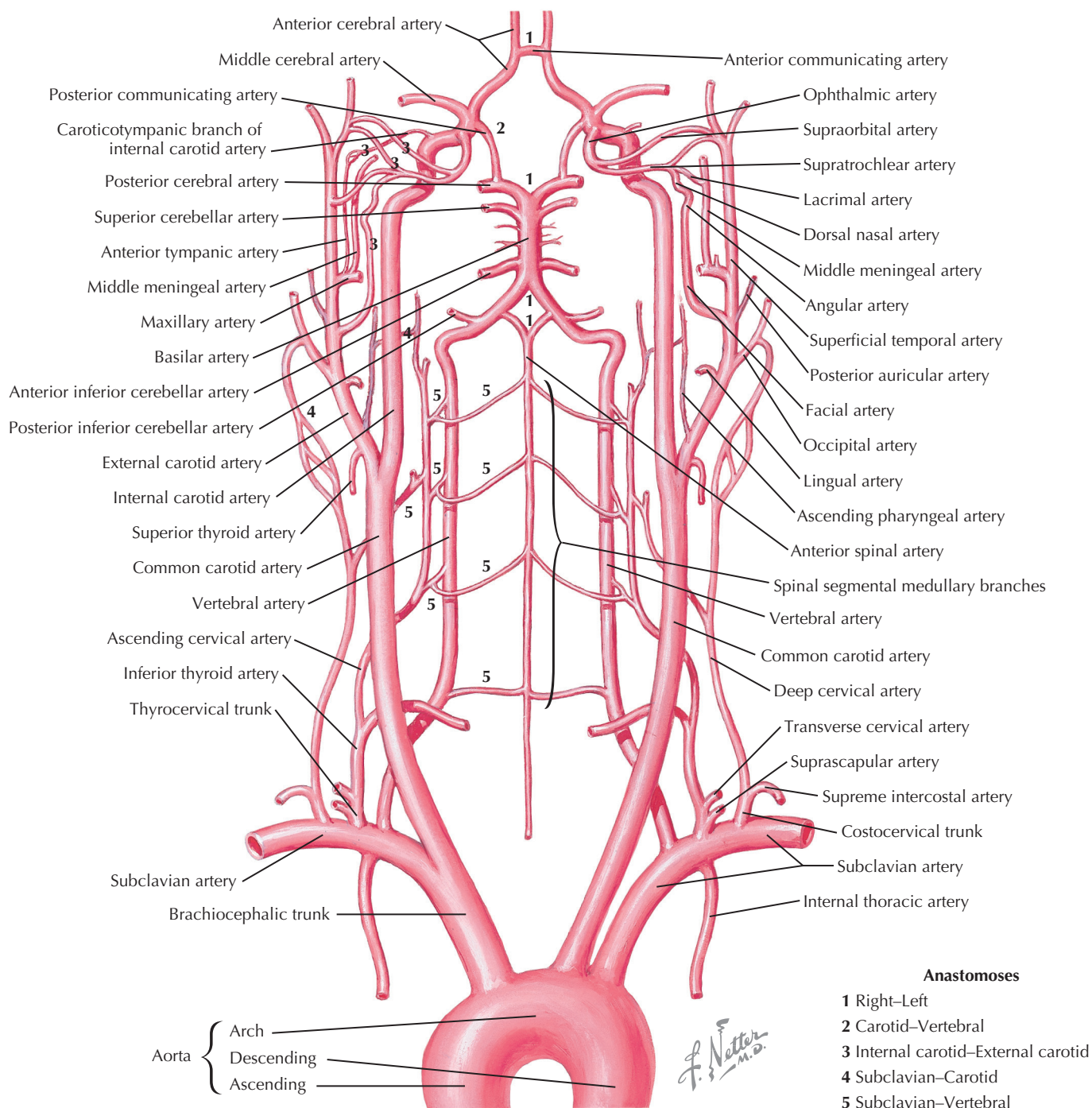


## 7.9 TYPES OF STROKES

There are two types of strokes, ischemic and hemorrhagic. The ischemic strokes include thrombotic strokes, embolic strokes, and hypoxic strokes. The hemorrhagic strokes include sub-

arachnoid hemorrhages (ruptured aneurysm) and intracerebral hemorrhages (hypertensive strokes or bleeds associated with anticoagulant medication).

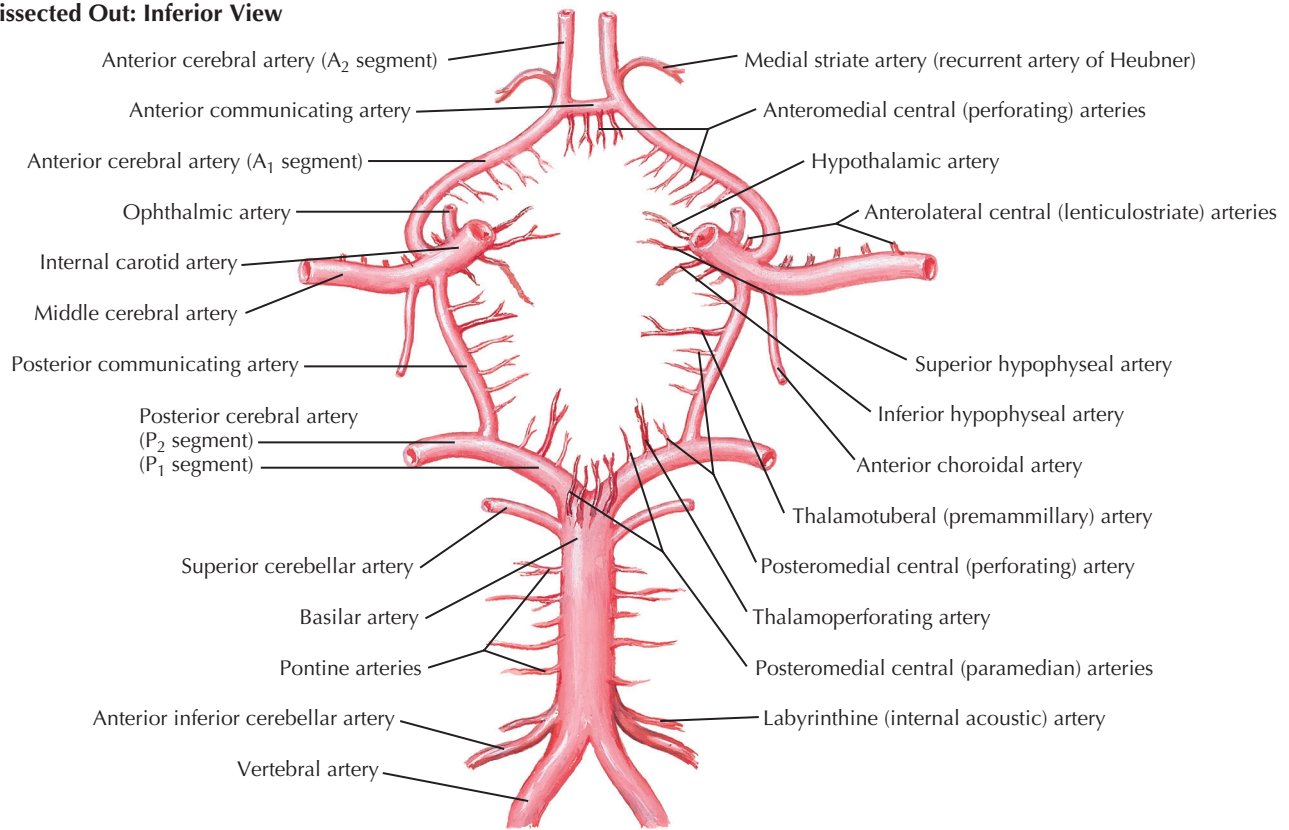
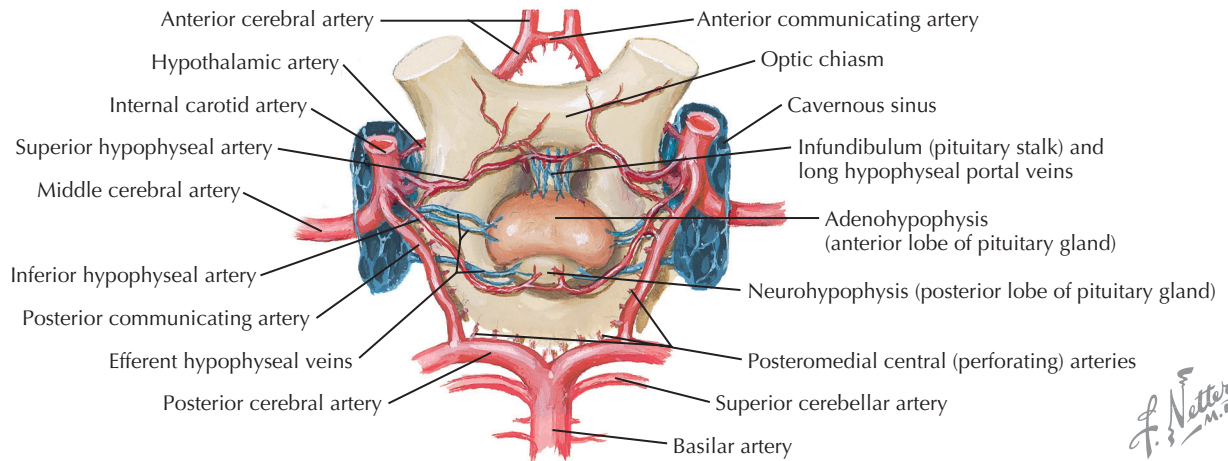




### 7.10 SCHEMATIC OF ARTERIES TO THE BRAIN

This schematic diagram shows the entire layout of the arterial blood supply to the brain, including anastomoses. The circle of Willis is present in the upper central portion of this sche-

matic. The relative separation of the anterior (MCA, ACA) and posterior (vertebrobasilar system, PCA) circulation is evident in this diagram. See [Videos 7-3](#) and [7-4](#).

**Vessels Dissected Out: Inferior View****Vessels in Situ: Inferior View**

*F. Netter M.D.*

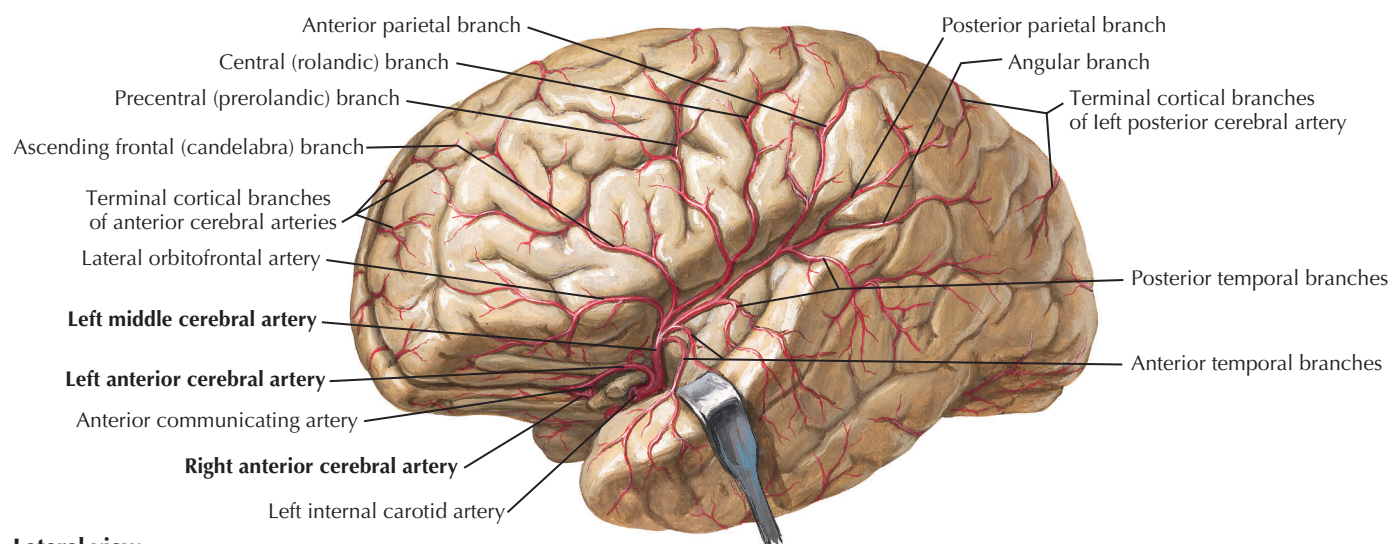
### 7.11 CIRCLE OF WILLIS: SCHEMATIC ILLUSTRATION AND VESSELS IN SITU

The circle of Willis surrounds the optic tracts, pituitary stalk, and basal hypothalamus. It includes the three sets of paired cerebral arteries plus the anterior communicating artery, interconnecting the ACAs, and the posterior communicating arteries, interconnecting the MCAs and PCAs. The free flow of arterial blood through the communicating arteries usually is insufficient to perfuse the brain adequately in the face of an occlusion to a major cerebral artery; the circle of Willis is fully patent and functional for free flow through the communicating arteries in only approximately 20% of individuals. The circle of Willis is the most common site of cerebral aneurysms.

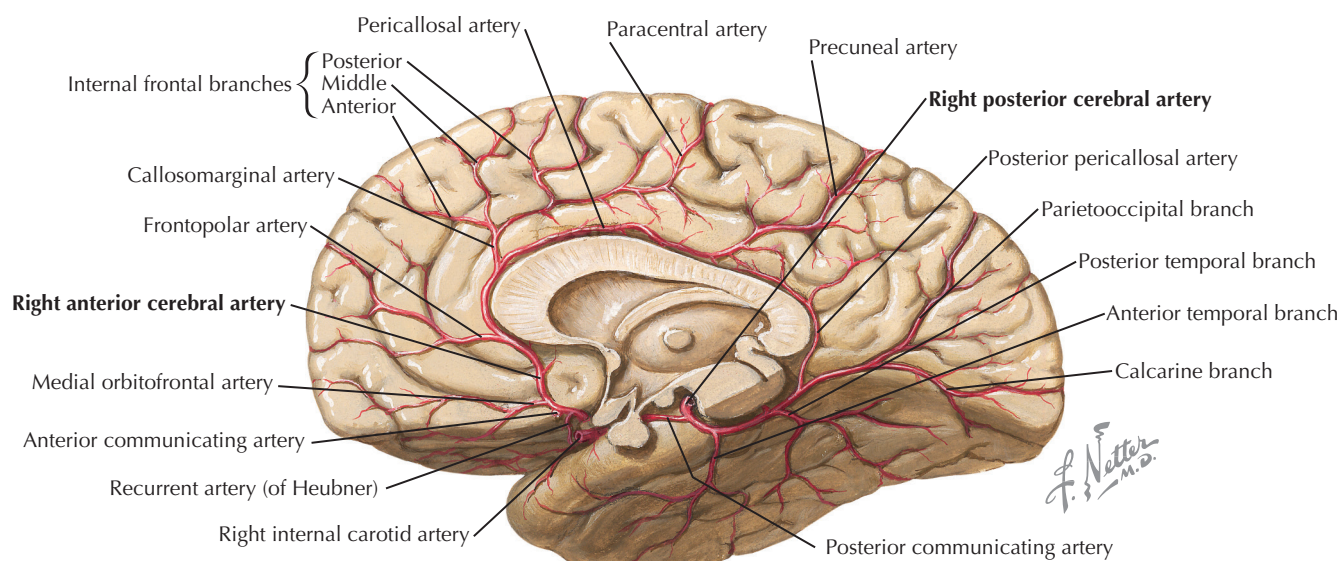
**CLINICAL POINT**

Saccular, or berry, aneurysms account for more than 80% of all intracranial aneurysms; they are outpouchings of cerebral arteries that probably form over a relatively short period of time (days to weeks). The most likely site of these berry aneurysms is at the junctions of arteries in the circle of Willis. Rupture of the aneurysm results in arterial bleeding into the cerebrospinal fluid (subarachnoid hemorrhage), which produces an acute, excruciating headache, nausea, vomiting, signs of meningeal irritation, and sometimes loss of consciousness. A sudden subarachnoid hemorrhage may be immediately fatal. Autopsy studies show that most cerebral aneurysms never rupture. Untreated ruptured aneurysms have approximately a one third likelihood of rebleeding within 2 months, sometimes with fatal results; other sequelae are cerebral infarction and vasospasm of the affected vessel. Treatment sometimes involves clipping the aneurysm or occluding it with coils or balloons.





A. Lateral view



B. Medial view

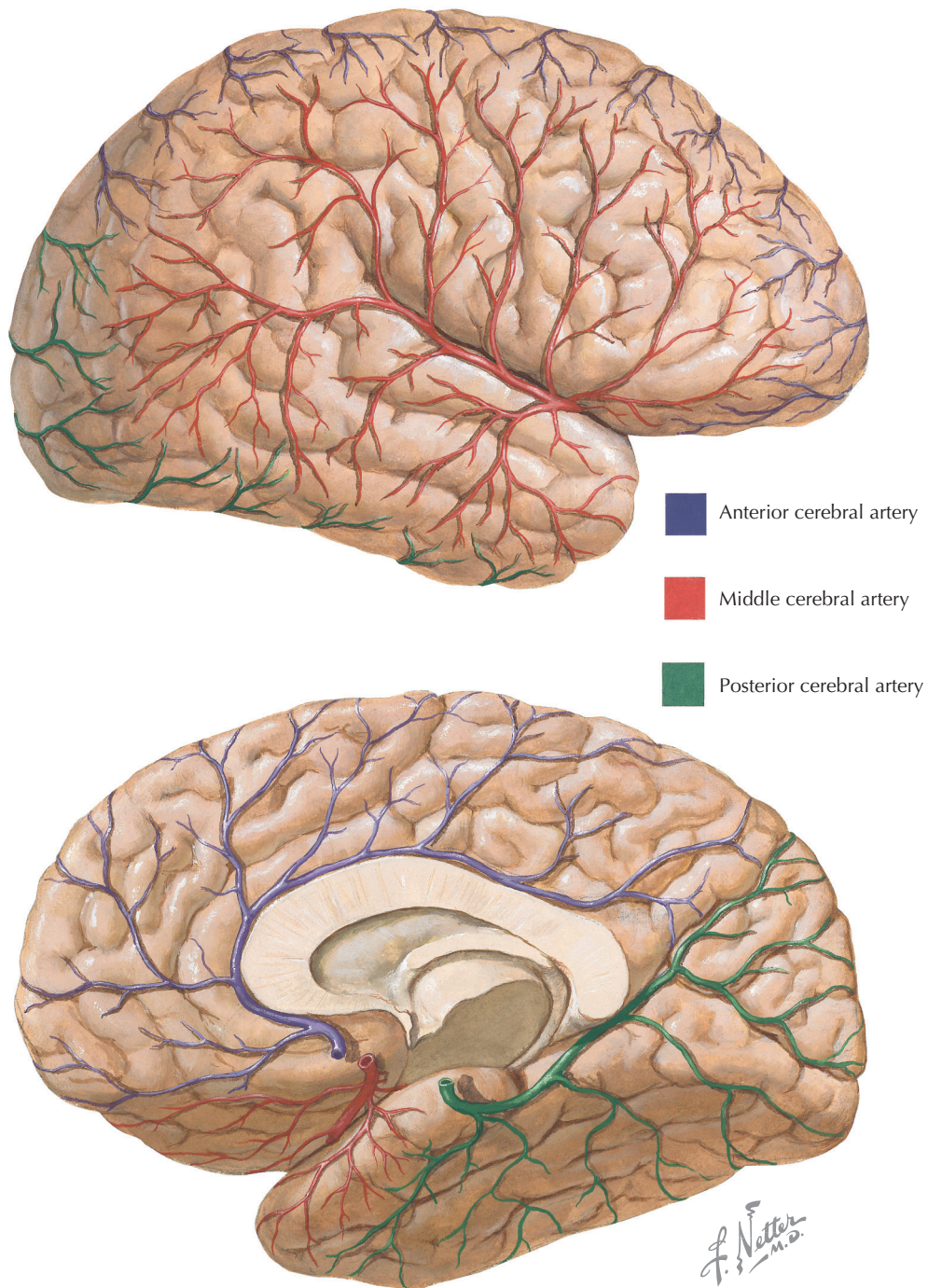
### 7.12 ARTERIAL DISTRIBUTION TO THE BRAIN: LATERAL AND MEDIAL VIEWS

**A,** The MCA sends named branches along the surface of the hemispheric convexity into the frontal and parietal lobes and into the anterior and middle regions of the temporal lobes. Occlusion disrupts sensory and motor functions in the contralateral body, especially the upper extremity, or in the entire contralateral body if the blood supply to the internal capsule is affected. **B,** The ACA distributes to the midline region of the frontal and parietal lobes. Occlusion disrupts sensory and motor functions in the contralateral lower extremity. The PCA distributes to the occipital lobe and the inferior surface of the temporal lobe. Occlusion disrupts mainly visual functions in the contralateral visual field.

#### CLINICAL POINT

The MCA is a continuation of the ICA, extending through the lateral fissure to supply branches to the convexity of the hemisphere, as well as penetrating branches. Cerebrovascular “strokes” appear in several forms. Approximately one third are atherosclerotic/sclerotic strokes (usually preceded by a transient ischemic attack); about one third are embolic strokes; close to 20% are lacunar (small distal) infarcts; 10% are cerebral hemorrhages; and a small percent are ruptured aneurysms or arteriovenous malformations. Lacunar infarcts are small infarcts (between 3 to 4  $\mu\text{m}$  and 2 cm in diameter) in small penetrating vessels supplying the putamen, caudate, internal capsule, thalamus, pons, and cerebral white matter. They occur most commonly as atherosclerosis-related infarcts, particularly in the presence of hypertension or diabetes. Symptoms are determined by which region of the brain is involved; they can include weakness, hemiplegia, contralateral loss of sensation, ataxia, and other symptoms.

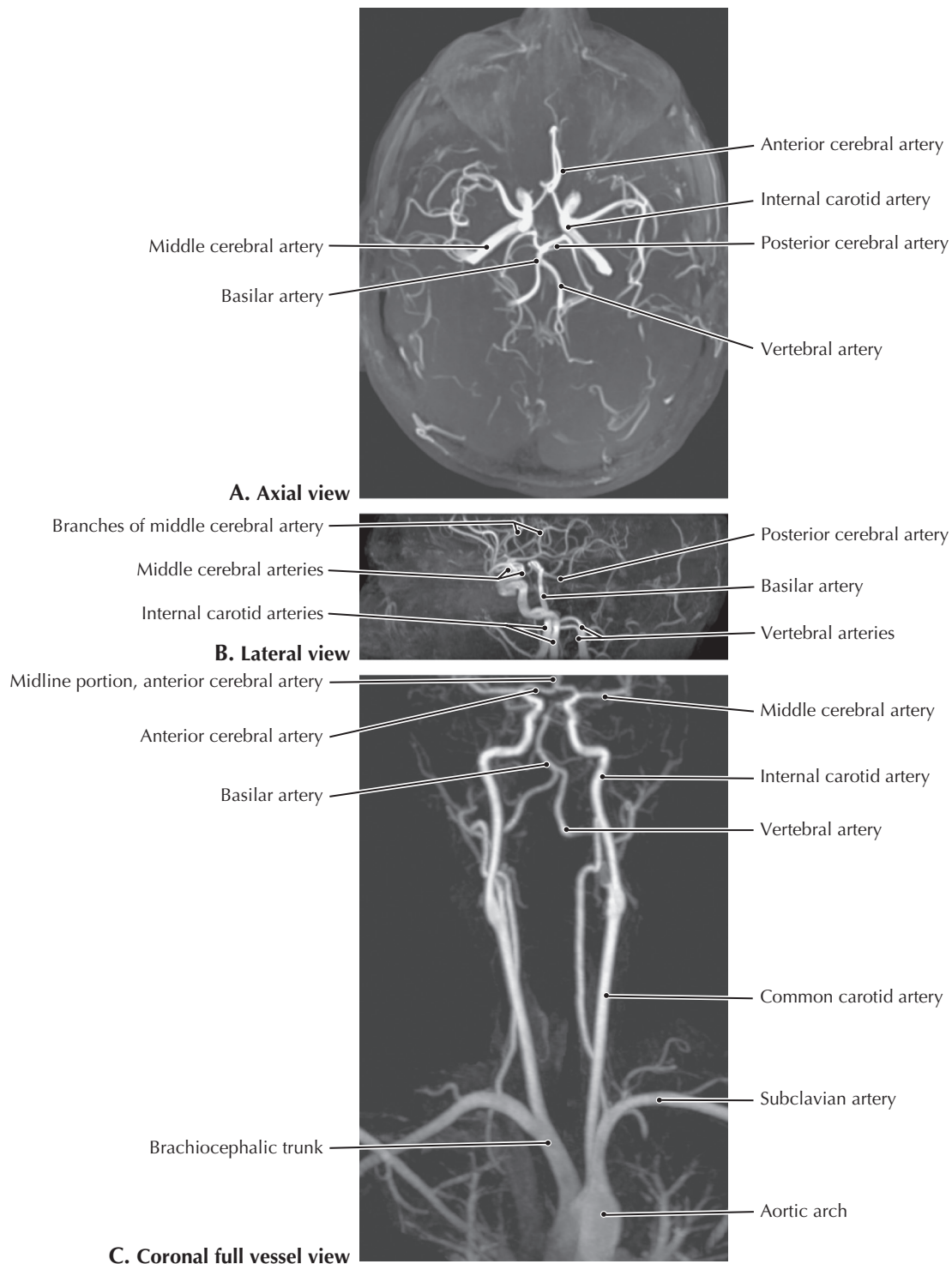




### 7.13 TERRITORIES OF THE CEREBRAL ARTERIES

The specific midline and lateral territories of distribution of the ACA, MCA, and PCA illustrate the exclusive zones sup-

plied by these major arteries and make particularly clear the watershed zones at the junctions of the major cerebral arteries.

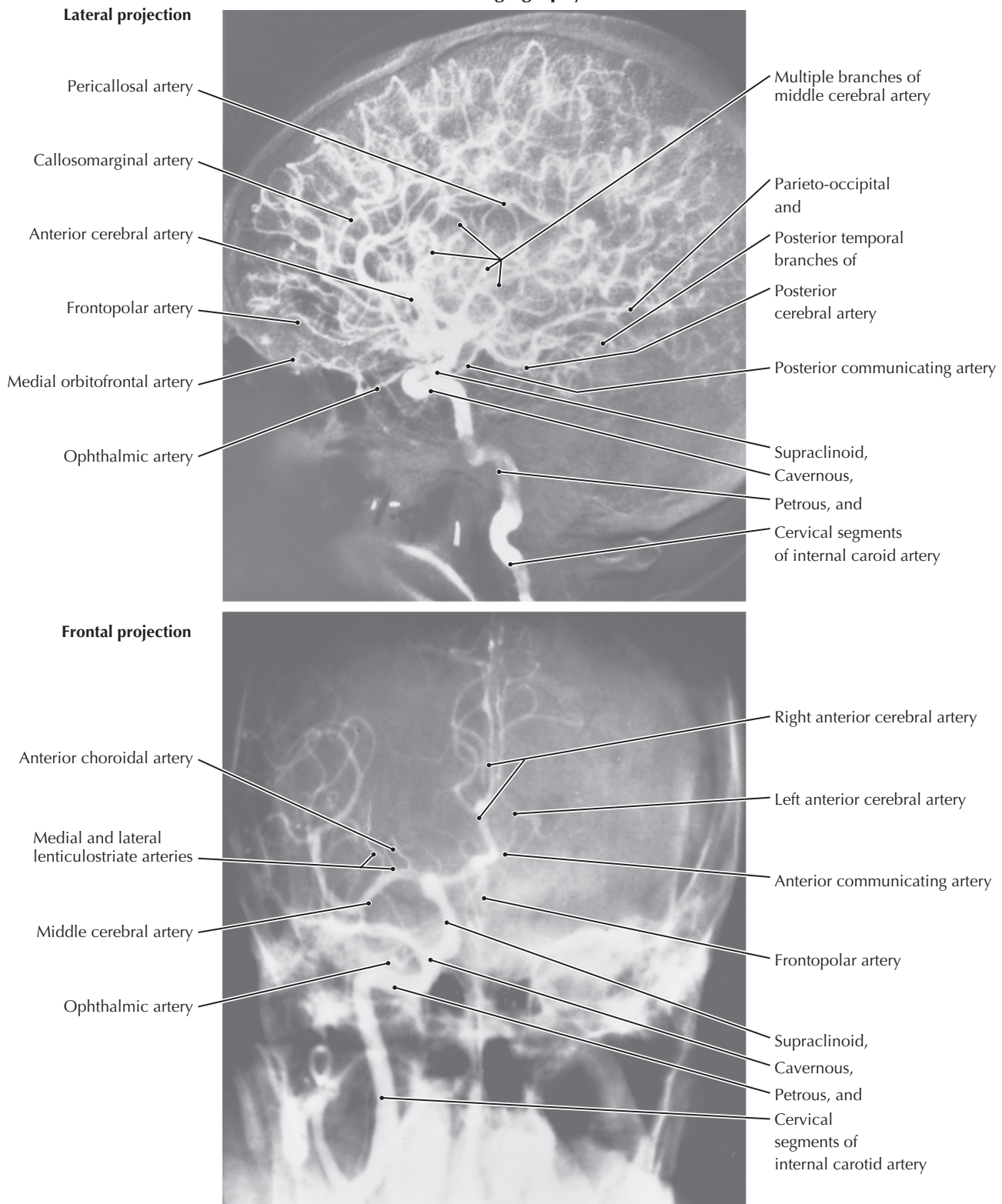


#### 7.14 MAGNETIC RESONANCE ANGIOGRAPHY: FRONTAL AND LATERAL VIEWS

A, Axial view. B, Lateral view. C, Coronal full vessel view. The technique of magnetic resonance angiography (MRA) exploits the properties of macroscopic blood flow to render images of cerebral blood vessels. Depending on the technique, the blood signal can be made to appear dark or bright; with conventional spin-echo pulse sequences, the blood vessels appear dark, and with gradient-echo pulse sequences, the blood vessels appear bright. There are two types of MRA that are

defined mainly by the two fundamental flow effects in magnetic resonance: time-of-flight phenomena based on magnitude effects and phase contrast phenomena, based on phase-shift effect. The MRAs in these images were made by using the technique that exploits signal enhancement due to the effects of time of flight. Positive flow contrast is generated by inflow effects, whereas the background (stationary tissue) is saturated by the rapid, repeated application of the radiofrequency pulses; thus the blood signal is higher than that of stationary tissue.

## Cerebral Angiography



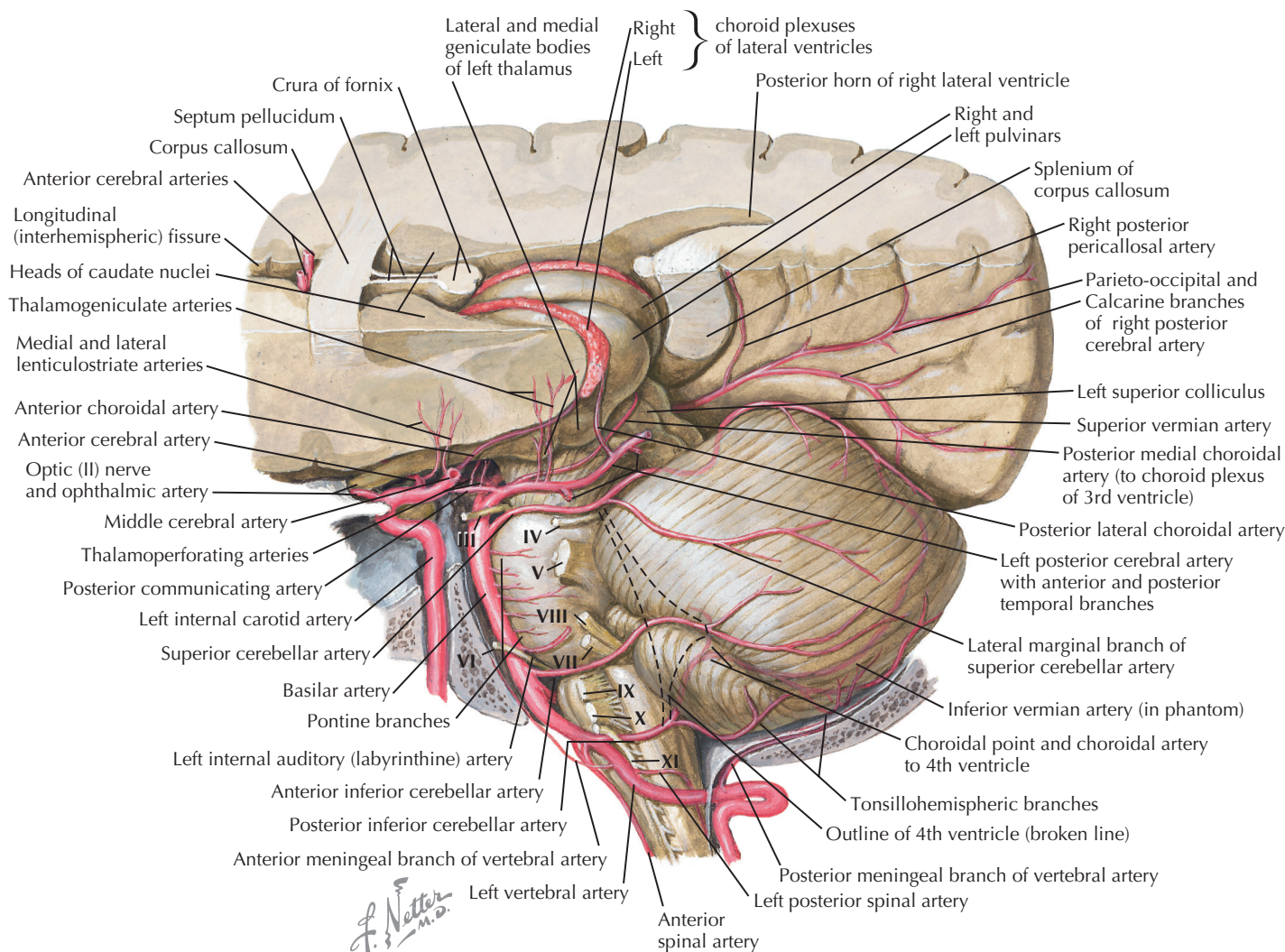
### 7.15 ANGIOGRAPHIC ANATOMY OF THE INTERNAL CAROTID CIRCULATION

The top plate is an angiogram that is a lateral view of the ICA circulation after injection of a radiopaque contrast agent into the ICA. The major branches of the ICA, particularly the ACA and MCA, are delineated. The bottom plate is an angiogram

that is a frontal view of the ICA circulation after injection of a radiopaque contrast agent into the common carotid artery. The major branches of this arterial system are delineated. MRA is used commonly to investigate the status of the cerebral arteries, but angiography with contrast agents can provide excellent anatomical details for teaching purposes.



## Arteries of Posterior Cranial Fossa



## 7.16 VERTEBROBASILAR ARTERIAL SYSTEM

The vertebral arteries unite at the midline to form the basilar artery. Medial penetrating branches extend into medial zones of the brain stem, supplying wedgelike territories. Infarcts in these branches can produce “alternating hemiplegias,” resulting in contralateral motor deficits (corticospinal system damage above the decussation of the pyramids), and ipsilateral brain stem/cranial nerve signs and symptoms. The vertebral and basilar arteries also give rise to larger short and long circumferential branches, such as the posterior inferior cerebellar artery (PICA), the anterior inferior cerebellar artery (AICA), and the superior cerebellar artery (SCA). Strokes in these arterial territories generally produce a constellation of ipsilateral brain stem sensory, motor, and autonomic symptoms and contralateral somatosensory symptoms. For example, an infarct in the vertebral artery or the PICA can result in loss of pain and temperature sensation on the con-

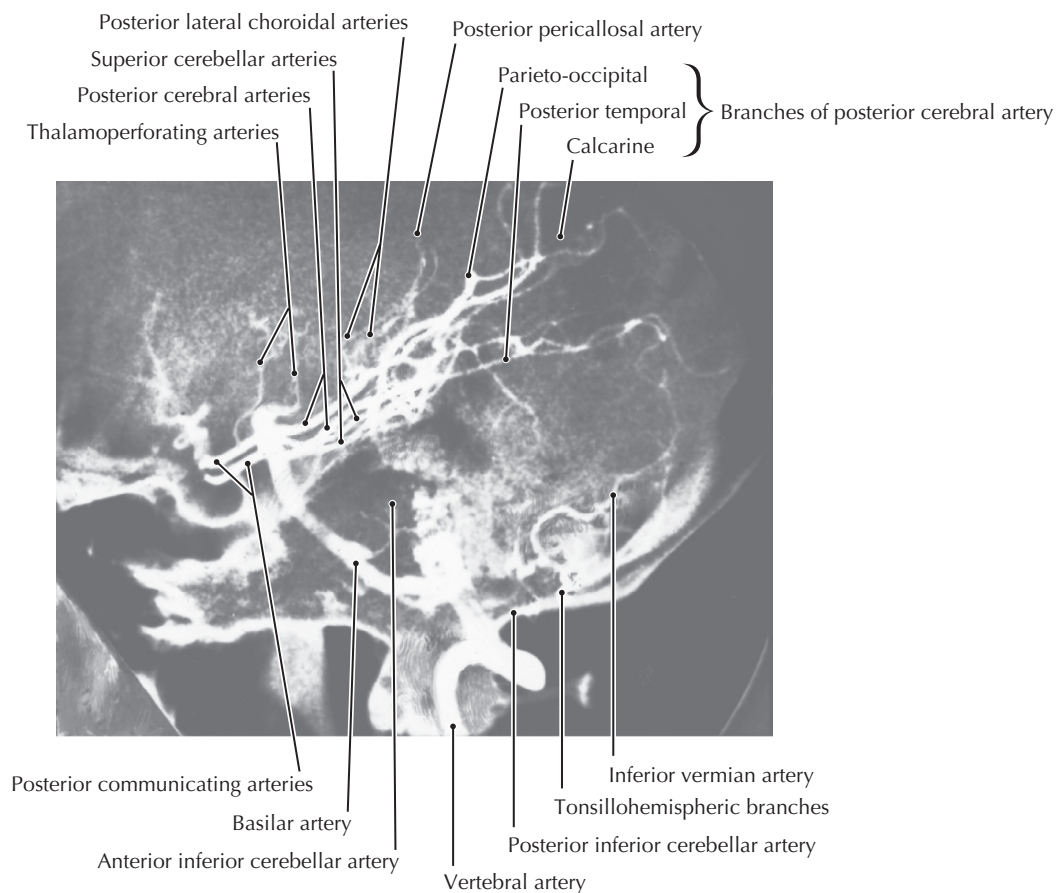
tralateral body and the ipsilateral face. The end branch of the basilar artery is the PCA, which distributes to the visual cortex and inferior temporal lobe. Occlusion results in contralateral hemianopsia.

## CLINICAL POINT

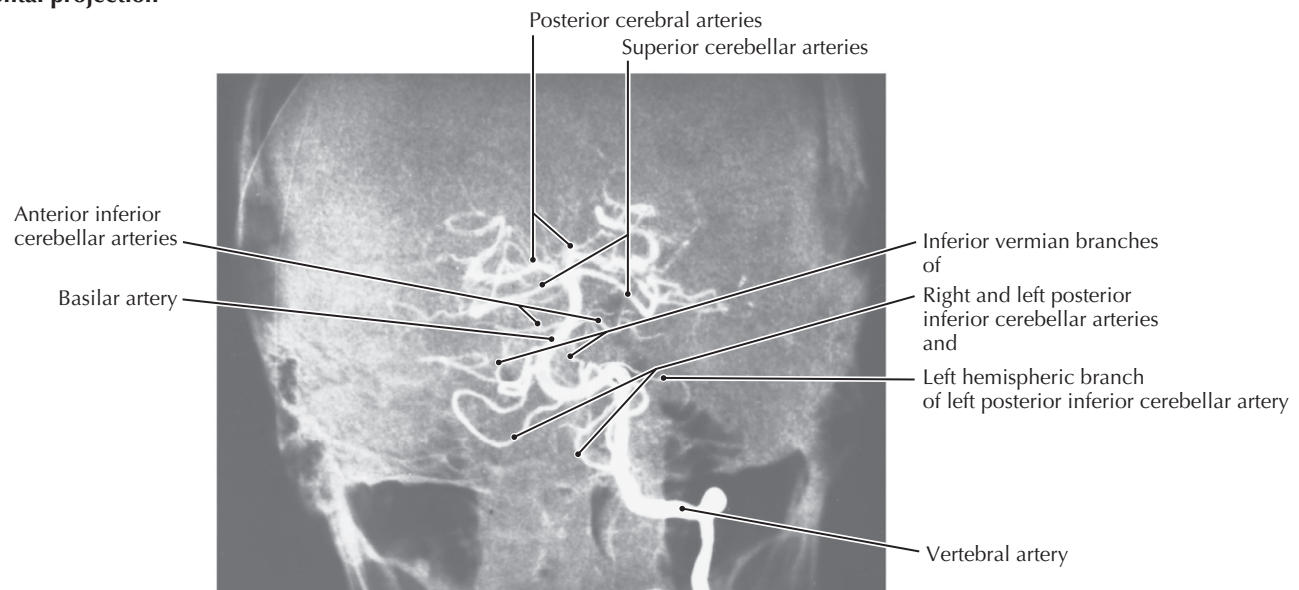
The vertebrobasilar system gives rise to several types of arterial branches. Those located most medially are the paramedian branches. An infarct in such a branch commonly involves ipsilateral damage to a cranial nerve and its function as well as contralateral hemiplegia because of involvement of the corticospinal tract before it decussates on its way to the spinal cord. These infarcts are known as alternating hemiplegias. The short and long circumferential arteries distribute into more lateral territories, and infarcts commonly result in a complex mixture of sensory, motor, and autonomic symptoms, as seen in the lateral medullary syndrome resulting from an infarct in the vertebral artery or the PICA on one side.

### Arteries of Posterior Cranial Fossa Vertebral Angiograms: Arterial Phase

#### A. Lateral projection



#### B. Frontal projection

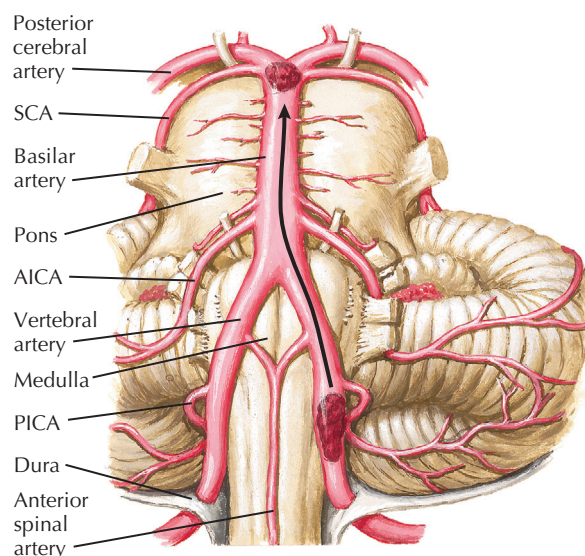


### 7.17 ANGIOGRAPHIC ANATOMY OF THE VERTEBROBASILAR SYSTEM

These figures show angiograms of both lateral and frontal views of the vertebrobasilar (posterior) circulation after injection

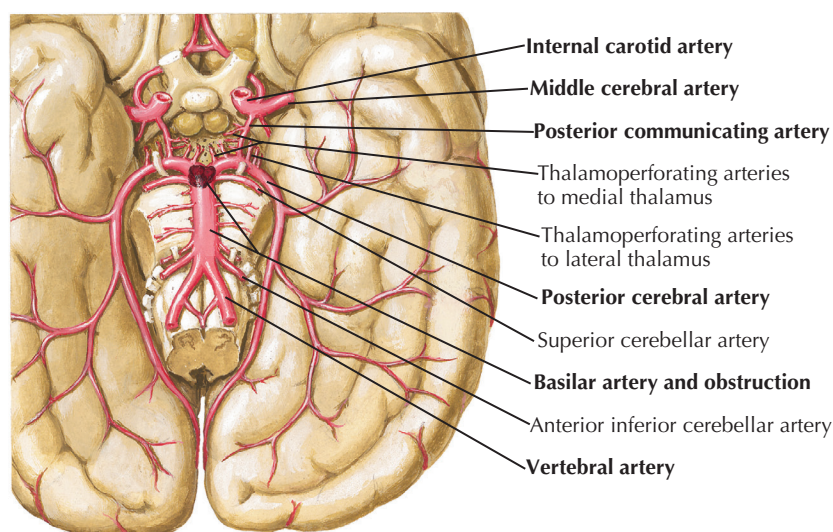
of a radiopaque contrast agent into the vertebral artery. The major arterial branches of this system are delineated.



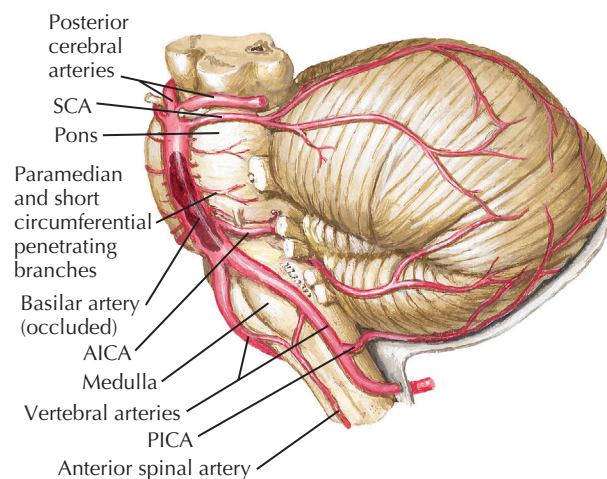


Intracranial obstruction of vertebral artery proximal to origin of posterior inferior cerebellar artery (PICA) may be compensated by preserved flow from contralateral vertebral artery. If PICA origin is blocked, lateral medullary syndrome (shown above) may result. Clot also may extend to block anterior spinal artery branch, causing hemiplegia, or embolization to basilar bifurcation may cause "top of basilar" syndrome.

A

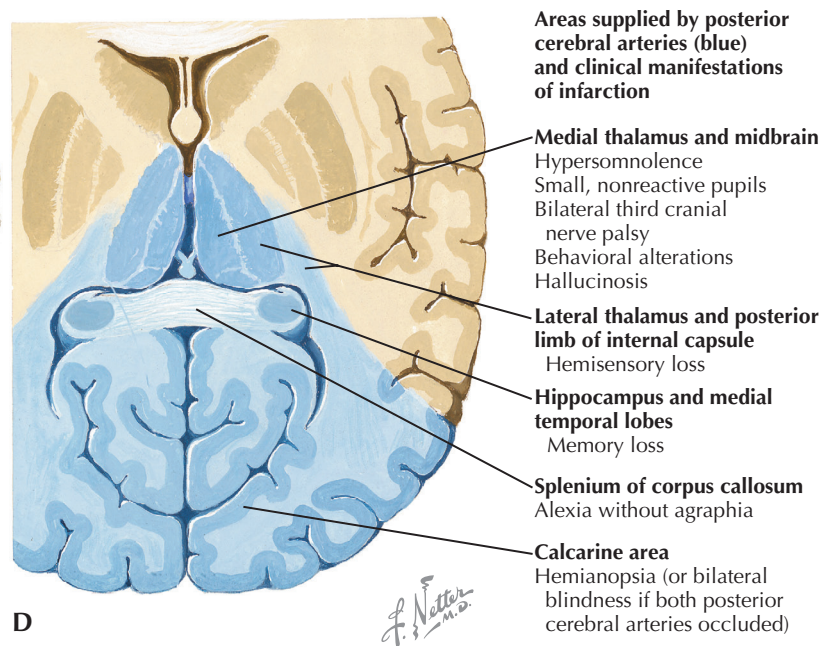


C



Collateral circulation via superior cerebellar (SCA), anterior inferior cerebellar (AICA), and posterior inferior cerebellar (PICA) arteries may partially compensate for basilar occlusion. Basilar artery has paramedian, short circumferential and long circumferential (AICA) and (SCA) penetrating branches. Occlusion of any or several of these branches may cause pontine infarction. Occlusion of AICA or PICA may also cause cerebellar infarction.

B



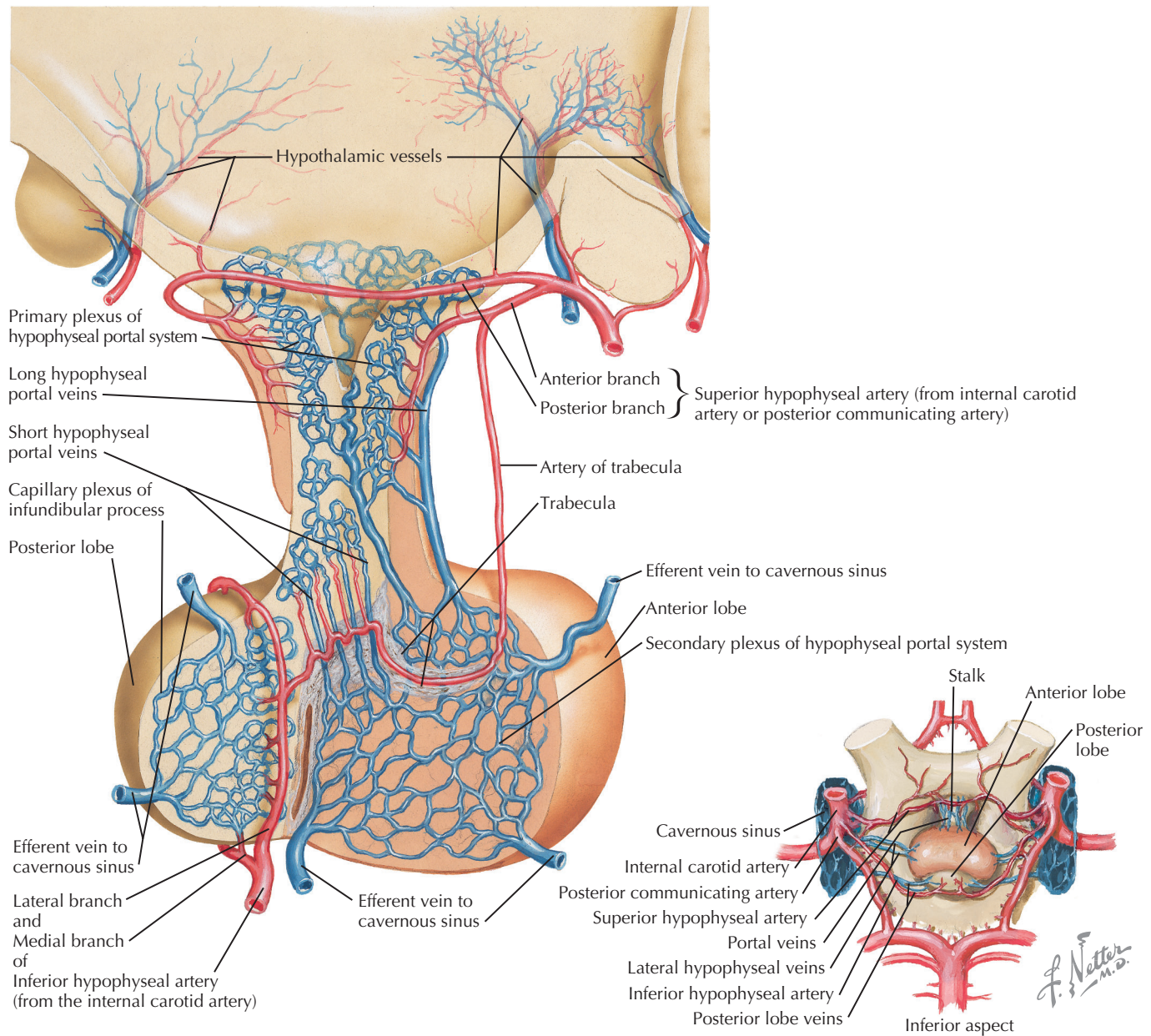
D

## 7.18 OCCLUSIVE SITES OF THE VERTEBROBASILAR SYSTEM

A. Arteries of the base of the brain stem, illustrating a vertebral artery/PICA occlusion, and a top of the basilar syndrome. B. Arteries of the brain stem in lateral view, showing potential collateral circulation among paramedian branches and short

and long circumferential branches. C. Vertebrobasilar arterial system with posterior cerebral artery end branches, illustrating a top of the basilar occlusion. D. The territories of brain supplied by the posterior cerebral arteries and the possible functional consequences of occlusion.



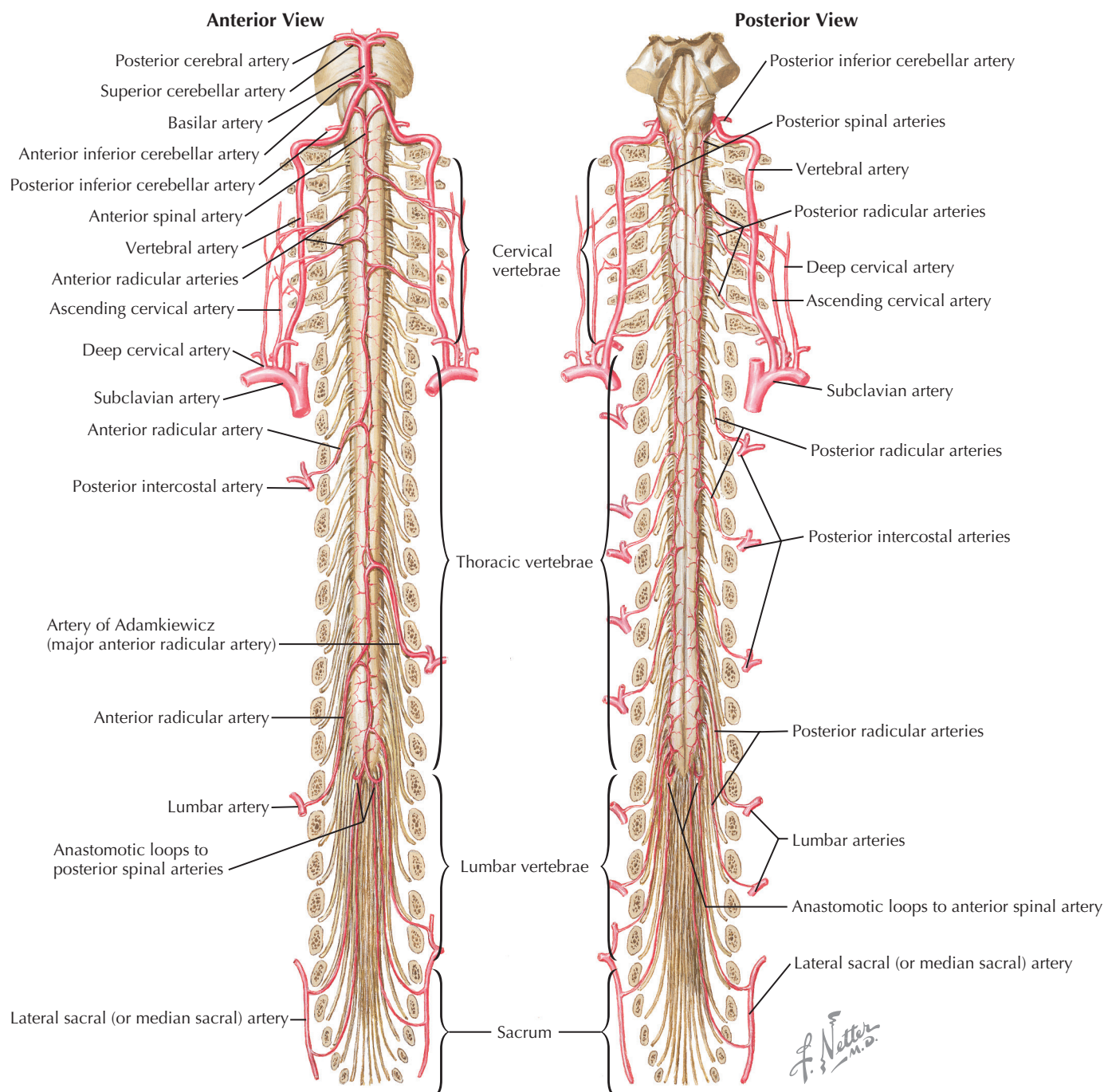


### 7.19 VASCULAR SUPPLY TO THE HYPOTHALAMUS AND THE PITUITARY GLAND

The superior hypophyseal arteries (from the ICA or the posterior communicating artery) supply the hypothalamus and infundibular stalk and anastomose with branches of the inferior hypophyseal artery (from the ICA). A unique aspect of this arterial distribution is the hypophyseal portal system, whose primary plexus derives from small arterioles and capillaries that then send branches into the anterior pituitary gland. This plexus allows neurons producing hypothalamic releasing factors and inhibitory factors to secrete these factors into the hypophyseal portal system, which delivers a very high concentration directly into the secondary plexus in the anterior pituitary. Thus, anterior pituitary cells are bathed in releasing and inhibitory factors in very high concentrations. This private vascular communication channel allows the hypothalamus to exert fine control, both directly and through feedback, over the secretion of anterior pituitary hormones.

#### CLINICAL POINT

The primary hypophyseal portal system coalesces into long hypophyseal portal veins that give rise to a secondary hypophyseal plexus. This arrangement allows the secretion of releasing and inhibitory factors from nerve endings, whose cell bodies are located in the hypothalamus and other structures, into a private vascular portal system, to be delivered to the pituitary cells in the anterior pituitary gland in extraordinarily high concentrations. The ultimate CNS control of the releasing and inhibitory factors profoundly influences neuroendocrine secretion and its downstream effects both target endocrine organs and the entire body. For example, corticotrophin releasing hormone or factor induces the release of adrenocorticotrophic hormone from the anterior pituitary, which is released into the systemic circulation and activates the adrenal cortex to release cortisol and other steroid hormones. This hypothalamo-pituitary-adrenal system helps to regulate glucose metabolism, insulin secretion, immune responses, adipose distribution, and a host of other vital functions. The corticotrophin releasing hormone neurons are under extensive regulatory control by neural inputs, hormonal feedback, and inflammatory mediators; these neurons help to orchestrate stress reactivity for the organism as a whole.

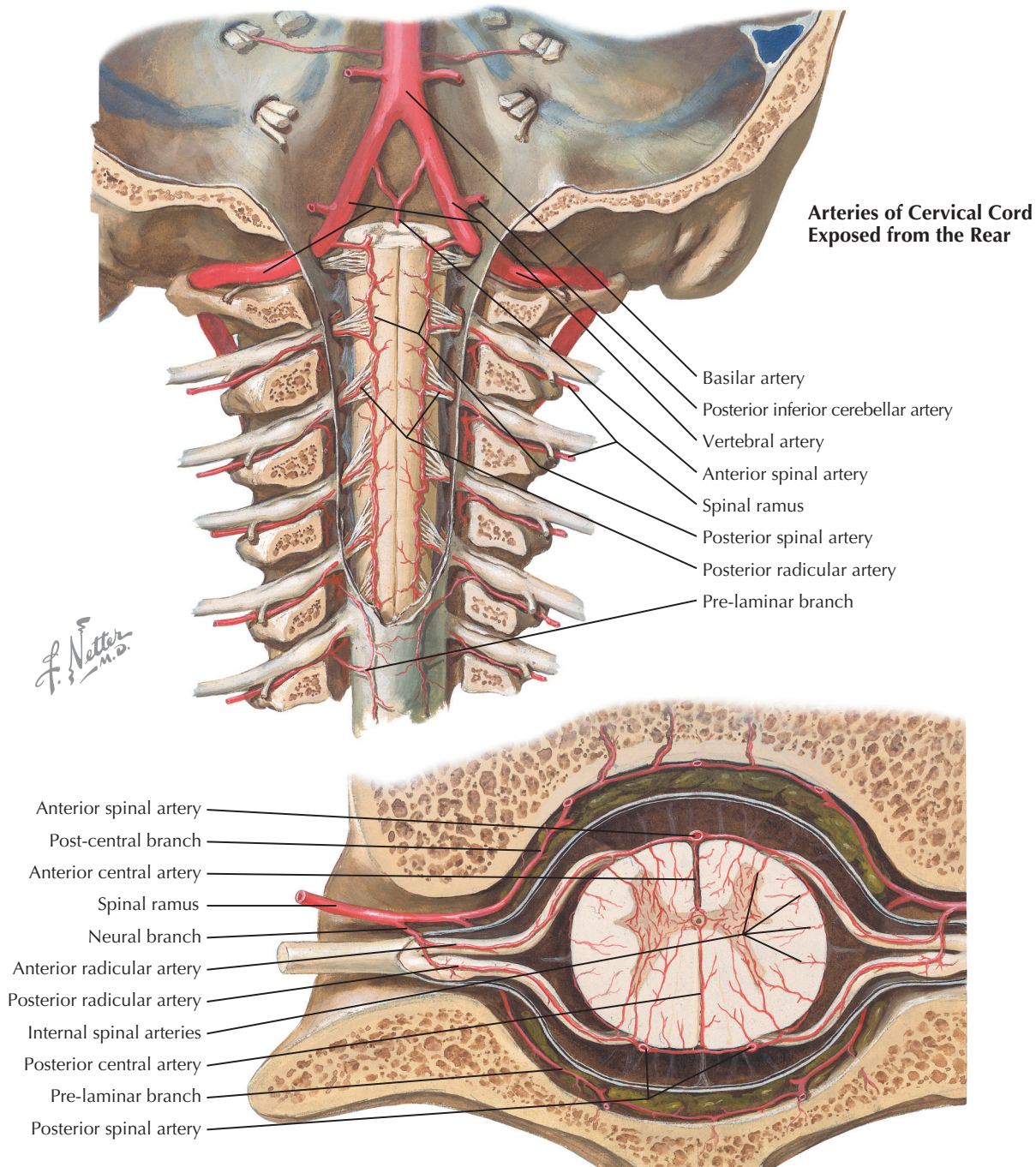


## 7.20 ARTERIAL BLOOD SUPPLY TO THE SPINAL CORD: LONGITUDINAL VIEW

The major arterial blood supply to the spinal cord derives from the anterior spinal artery and the paired posterior spinal arteries, both branches of the vertebral artery. The actual blood flow through these arteries, derived from the posterior circulation, is inadequate to maintain the spinal cord caudally beyond the cervical segments. Radicular arteries, deriving

from the aorta, provide major anastomoses with the anterior and posterior spinal arteries and supplement the blood flow to the spinal cord. The largest of these anterior radicular arteries, often from the L2 region, is the artery of Adamkiewicz. Impaired blood flow through these critical radicular arteries, especially during surgical procedures that involve abrupt disruption of blood flow through the aorta, can result in spinal cord infarct.



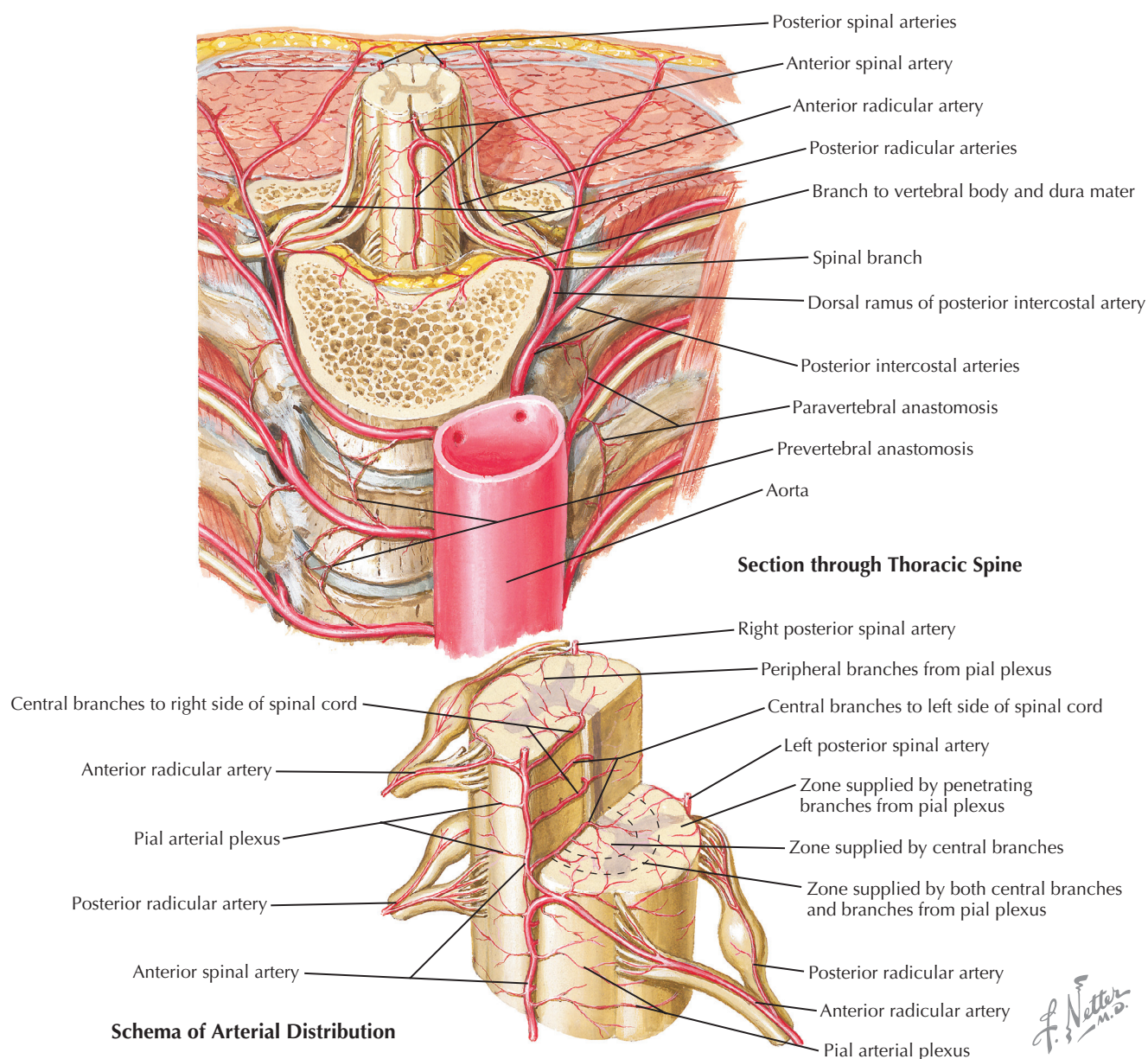


### 7.21 ANTERIOR AND POSTERIOR SPINAL ARTERIES AND THEIR DISTRIBUTION

The anterior and posterior spinal arteries travel in the sub-arachnoid space and send branches into the spinal cord. The anterior spinal artery sends alternating branches into the anterior median fissure to supply the anterior two thirds of the spinal cord. Occlusion of one of these branches can result in ipsilateral flaccid paralysis in muscles supplied by the affected segments, ipsilateral spastic paralysis below the affected level

(resulting from upper motor neuron axonal damage), and contralateral loss of pain and temperature sensation below the affected level (resulting from damage to the anterolateral spinothalamic/spinoreticular system). The posterior spinal artery branches supply the dorsal third of the spinal cord. Occlusion affects the ipsilateral perception of fine discriminative touch, vibratory sensation, and joint position sense below the level of the lesion (resulting from damage to fasciculi gracilis and cuneatus, the dorsal columns).





*F. Netter M.D.*

## 7.22 ARTERIAL SUPPLY TO THE SPINAL CORD: CROSS-SECTIONAL VIEW

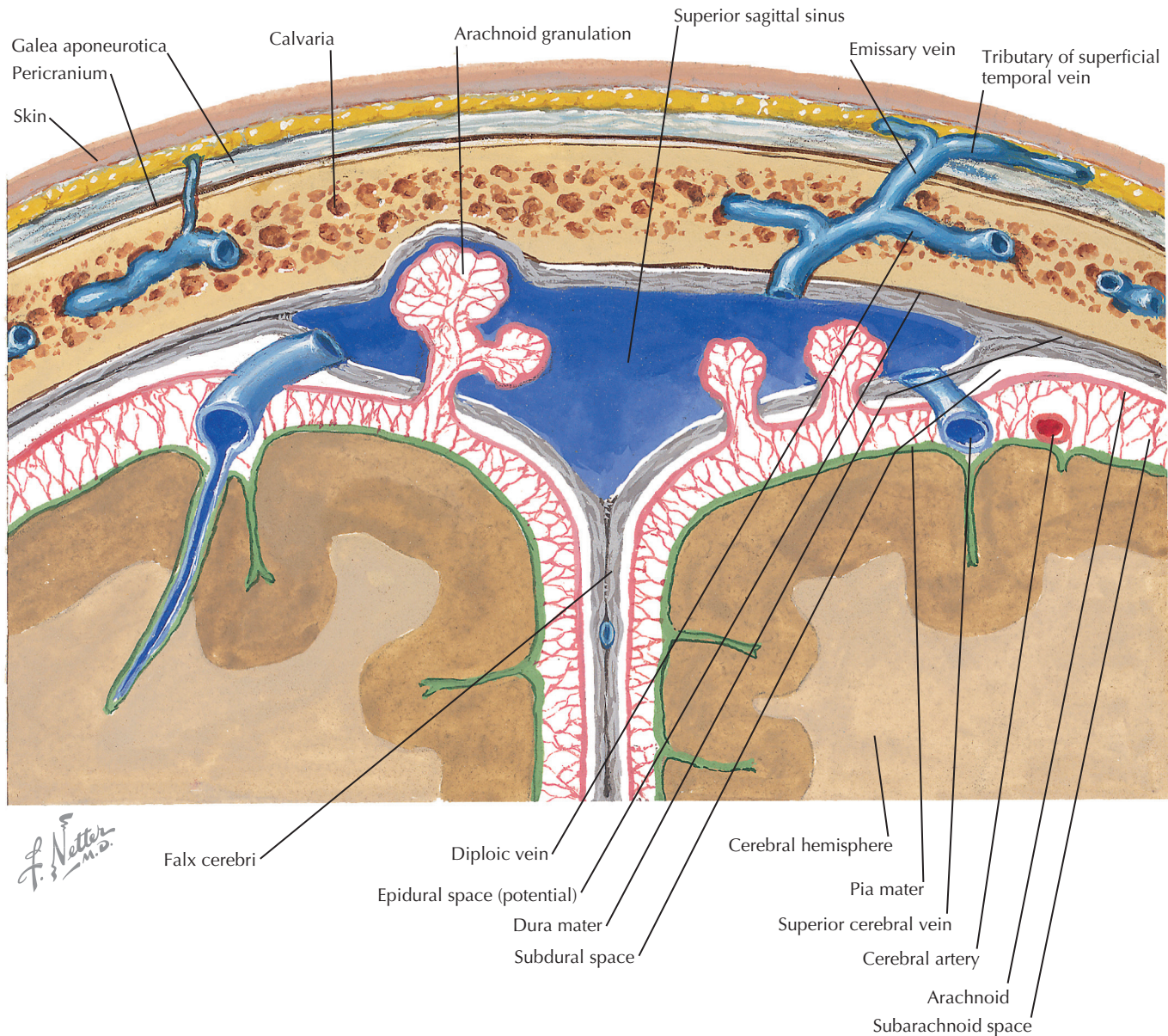
The major contribution to the arterial blood supply of the spinal cord below the cervical segments derives from the radicular arteries (*top*). This intercostal blood supply also distributes to adjacent bony and muscular structures. The penetrating vessels supplying the spinal cord derive from central branches of the anterior spinal artery and from a pial plexus of vessels that surround the exterior of the spinal cord.

### CLINICAL POINT

Alternating branches arise from the anterior spinal artery into the anterior two thirds of the spinal cord. Following an infarct in the

anterior spinal artery, acute radiating leg pain is experienced. Depending on the level of insult, acute flaccid paraparesis or quadraparesis occurs, resolving to spastic paraparesis or quadraparesis with hyperreflexia as the result of the upper motor neuron lesion resulting from damage to the bilateral lateral funiculi. Only at the level of the infarct, where lower motor neurons are lost, does flaccid paralysis remain, along with hyporeflexia. Bilateral plantar extensor responses are seen. Bilateral loss of pain and temperature sensation is seen because of ischemia to the anterolateral territory of the spinothalamic/spinoreticular protopathic system. Descending fibers for control of the bladder and bowel travel in the lateral funiculus and are damaged by an anterior artery infarct. In a lesion of the anterior spinal artery above the T1 level, bilateral damage to descending central sympathetic fibers regulating T1 intermediolateral cell column outflow produces bilateral Horner's syndrome, with bilateral ptosis, myosis, and anhidrosis.





## VENOUS SYSTEM

### 7.23 MENINGES AND SUPERFICIAL CEREBRAL VEINS

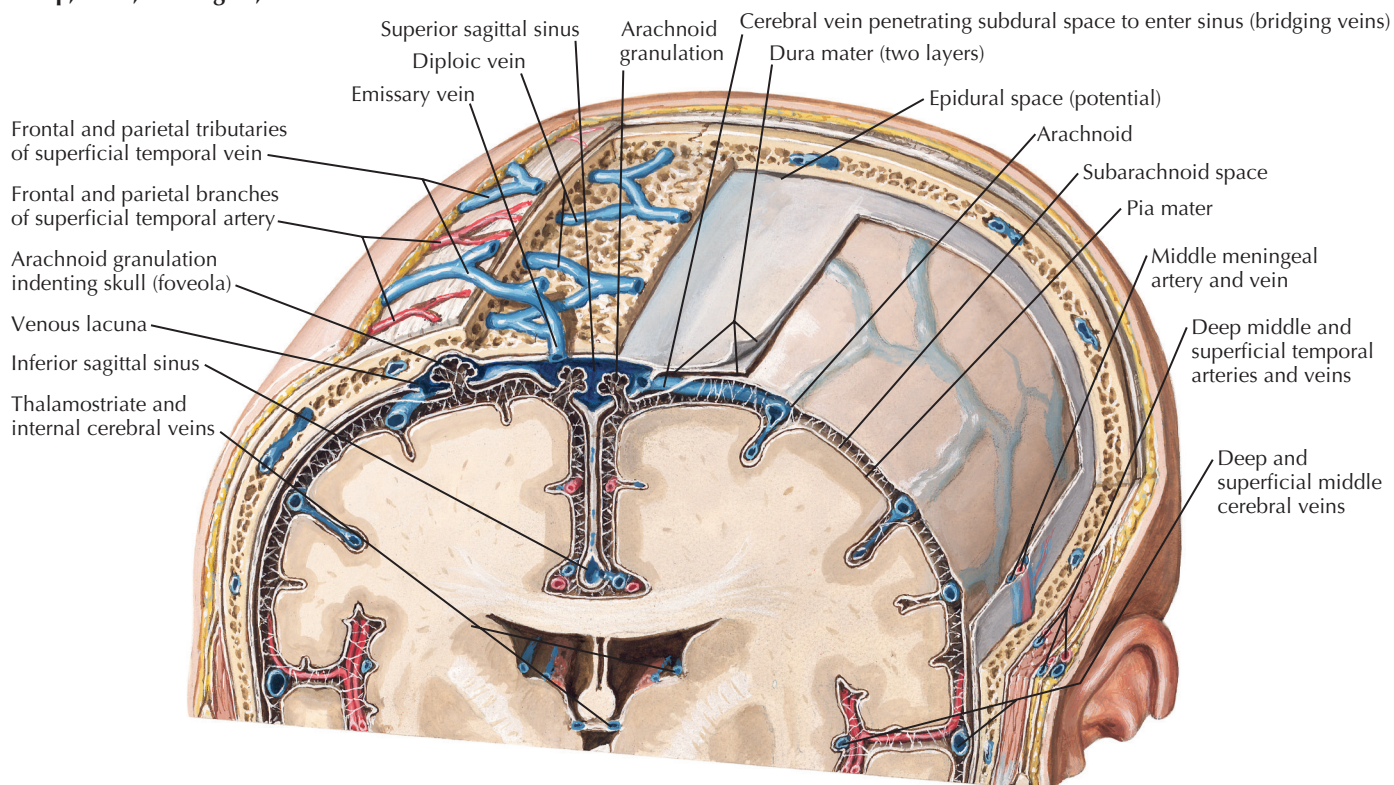
The superior sagittal sinus and other dural sinuses receive venous blood from a variety of veins, including superficial cerebral veins draining blood from the cortical surface, meningeal veins draining blood from the meninges, diploic veins draining blood from channels located between the inner and outer tables of the calvaria, and emissary veins, which link the venous sinuses and diploic veins with veins on the surface of the skull. These channels do not have valves and permit free communication between these venous systems and the venous sinuses. This is a significant factor in the possible spread of infections from foci outside the cranium to the venous sinuses. Recent studies demonstrate a lymphatic drainage network for the meningeal system.

#### CLINICAL POINT

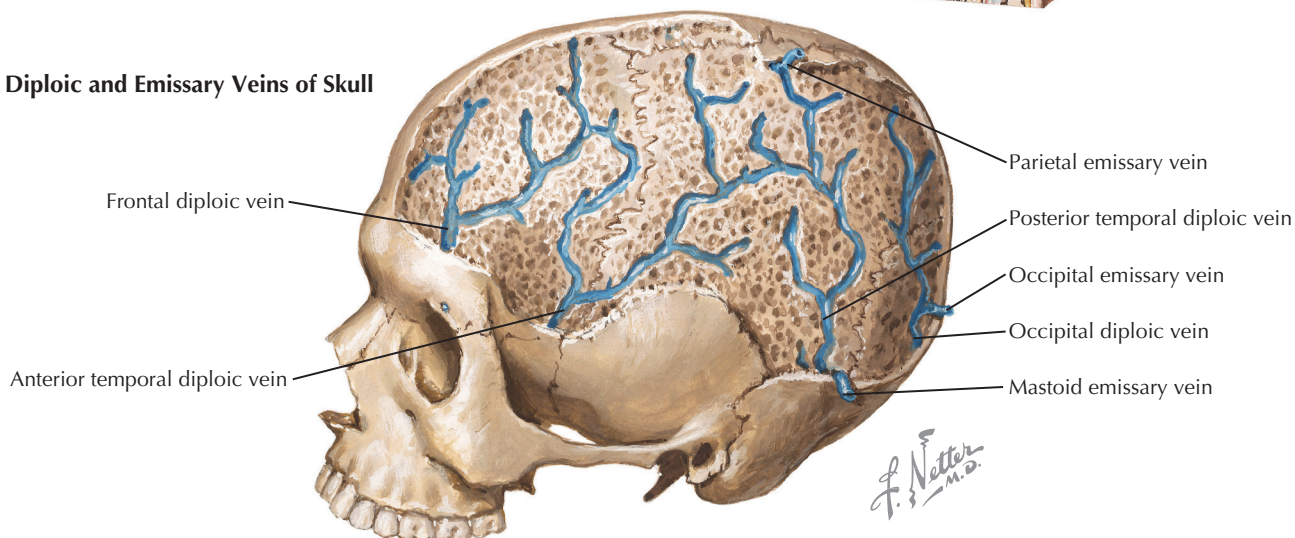
Arachnoid granulations act as one-way valves that convey cerebrospinal fluid into the dural sinus, channeling it back into the venous circulation. The cerebral veins also extend across the subarachnoid space and enter into the superior sagittal sinus. With severe head trauma, these bridging veins can be torn, with resultant venous bleeding into the subdural space; this bleed dissects the dura from the arachnoid and becomes a space-occupying mass. It also brings about cerebral edema and swelling. Acute subdural hematomas can be life-threatening, especially in young individuals with head trauma. Chronic subdural hematomas often occur in the elderly with relatively minor trauma; the bridging veins tear because of some mild atrophy of the underlying hemisphere, making the course of the bridging veins more extended and more vulnerable to tearing. Slow accumulation of subdural blood eventually can result in increased intracranial pressure with headache, lethargy, confusion, seizures, and focal neurological abnormalities. Surgical drainage is often performed for large subdural hematomas, whereas small hematomas usually regress naturally in the elderly.



### Scalp, Skull, Meningeal, and Cerebral Blood Vessels



### Diploic and Emissary Veins of Skull

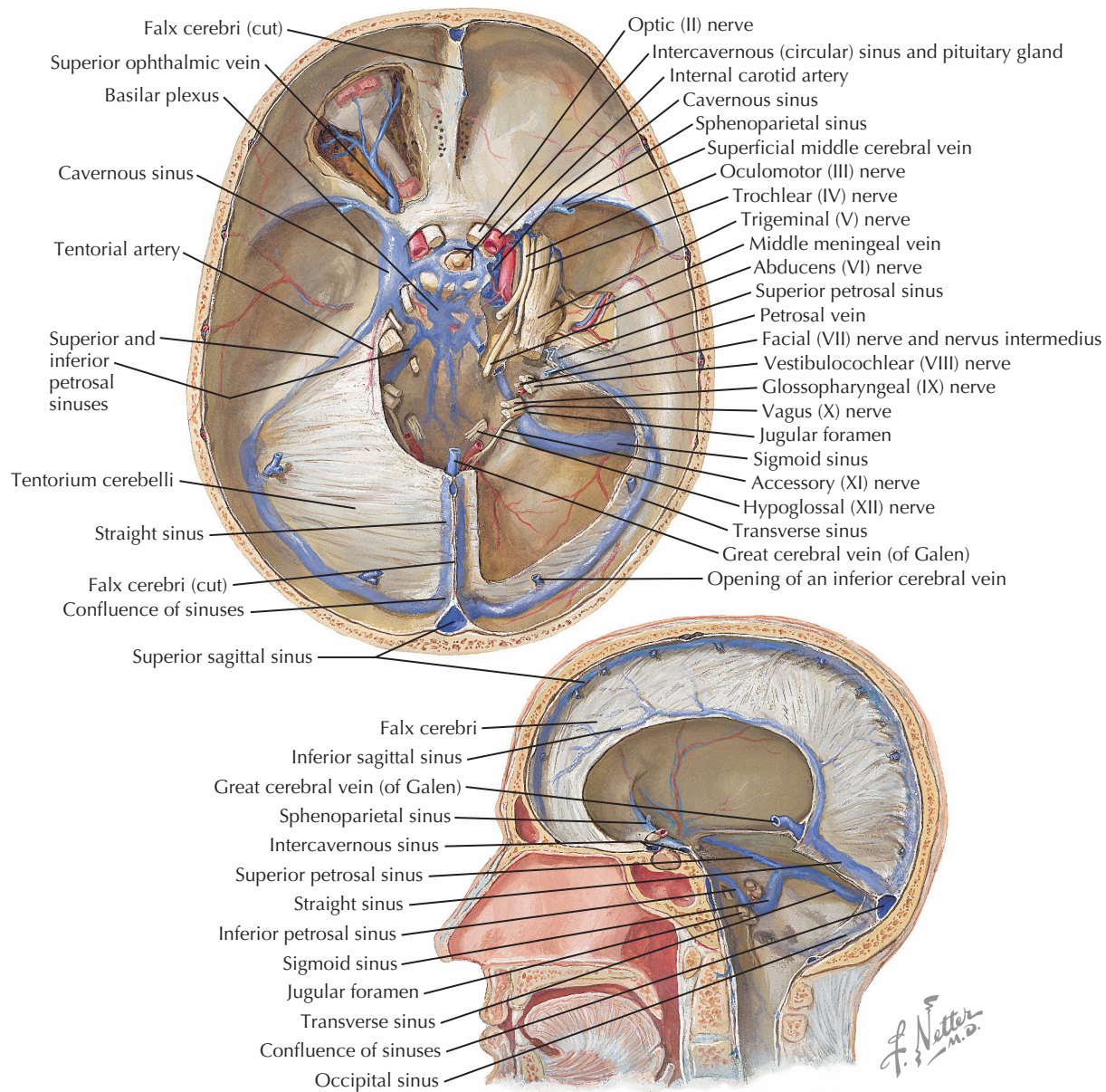


### 7.24 VEINS: SUPERFICIAL CEREBRAL, MENINGEAL, DIPLOIC, AND EMISSARY

Venous blood drains from the skull, the meninges, and the cerebral cortex into the superior sagittal sinus and other dural

sinuses. This is a point of vulnerability where potential infections and contamination from the more superficial venous drainage networks can be allowed into the central venous sinus channels.





## 7.25 VENOUS SINUSES

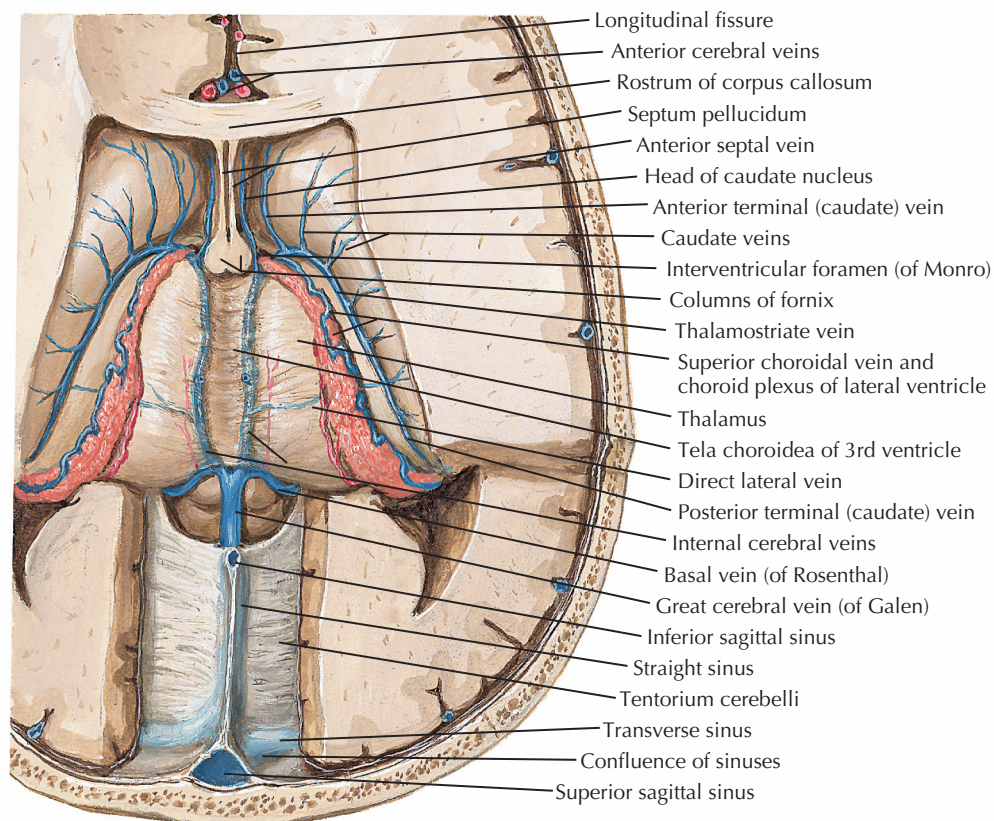
The falx cerebri and tentorium cerebelli, protrusions of fused inner and outer dural membranes, confine the anterior, middle, and posterior fossae of the skull. Outer (superior sagittal) and inner (inferior sagittal) venous channels, found in split layers of the dura, drain blood from the superficial and deep regions of the central nervous system, respectively, into the jugular veins. The great cerebral vein of Galen and the straight sinus merge with the transverse sinus into the confluence of sinuses to drain the deep, more posterior regions of the central nervous system. Infection can be introduced into the cerebral circulation through these sinuses. Venous sinus thrombosis can cause stasis (a backup of the venous pressure), which results in inadequate perfusion of the regions where drainage should occur. The protrusions of dura, such as the tentorium cerebelli and falx cerebri, are tough, rigid membranes through which portions of the brain can herniate when intracranial pressure increases.

### CLINICAL POINT

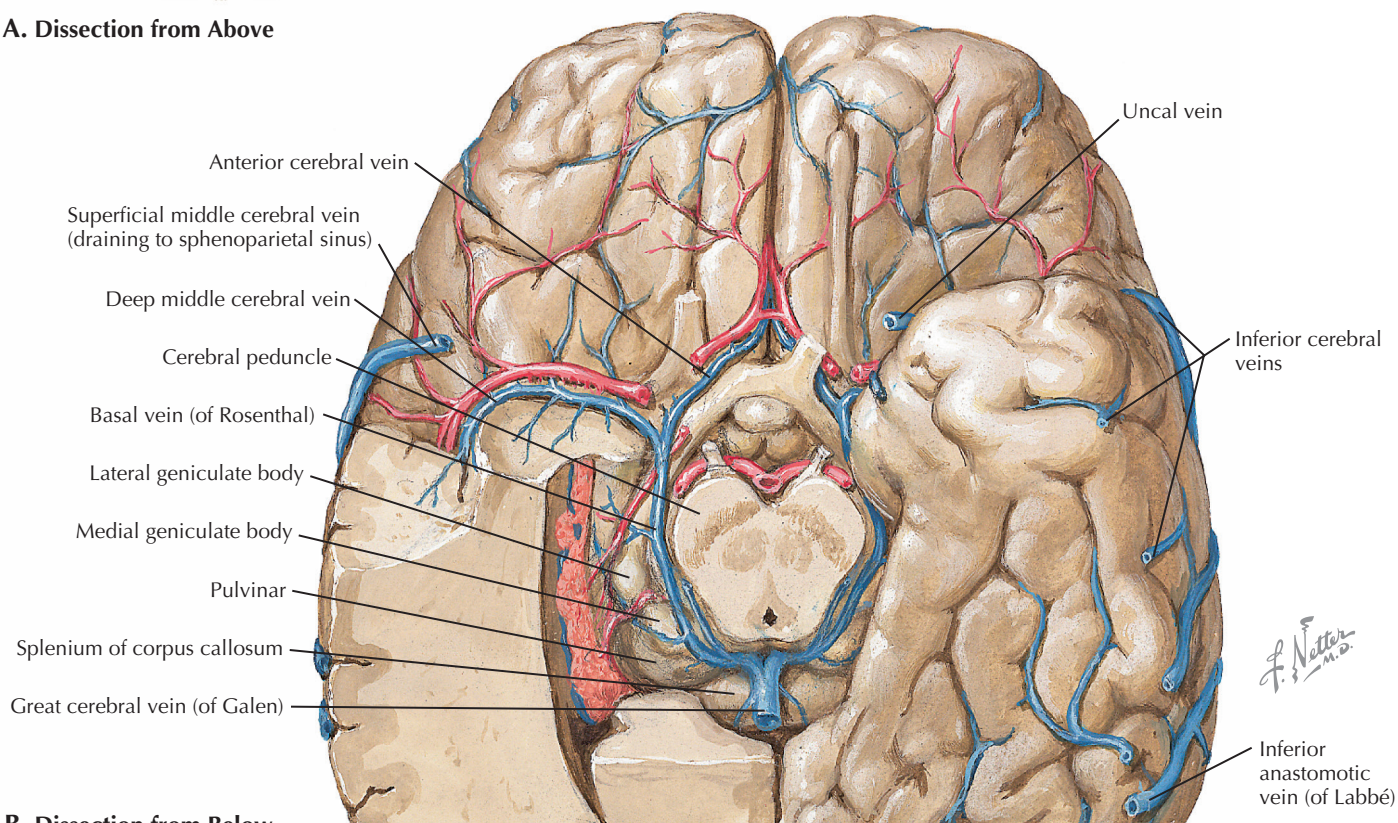
Venous sinus thrombosis commonly occurs with infection. Cavernous sinus thrombosis can occur as the result of infection in the paranasal sinuses or middle ear or following a furuncle in the region of the face. Anterior cavernous sinus thrombosis can result in severe pain and headache, ipsilateral visual loss, exophthalmos (protrusion of the eyeball), edema of the eyeball (chemosis), and palsies of the extraocular nerves (III, IV, VI) and VI (ophthalmic division) that traverse the sinus. This lesion can expand to cause hemiparesis and can involve the interconnected cavernous sinus of the other side, the superior petrosal sinuses, and other venous structures.

The petrosal sinuses can undergo a process of thrombosis caused by the spread of infection in the middle ear. An inferior petrosal sinus thrombosis may cause damage to the VI (abducens) nerve; a superior petrosal sinus thrombosis can result in damage to the semilunar ganglion, producing facial pain. If the transverse sinus is thrombosed, cranial nerve deficits in nerves IX, X, and XI may occur.





**A. Dissection from Above**



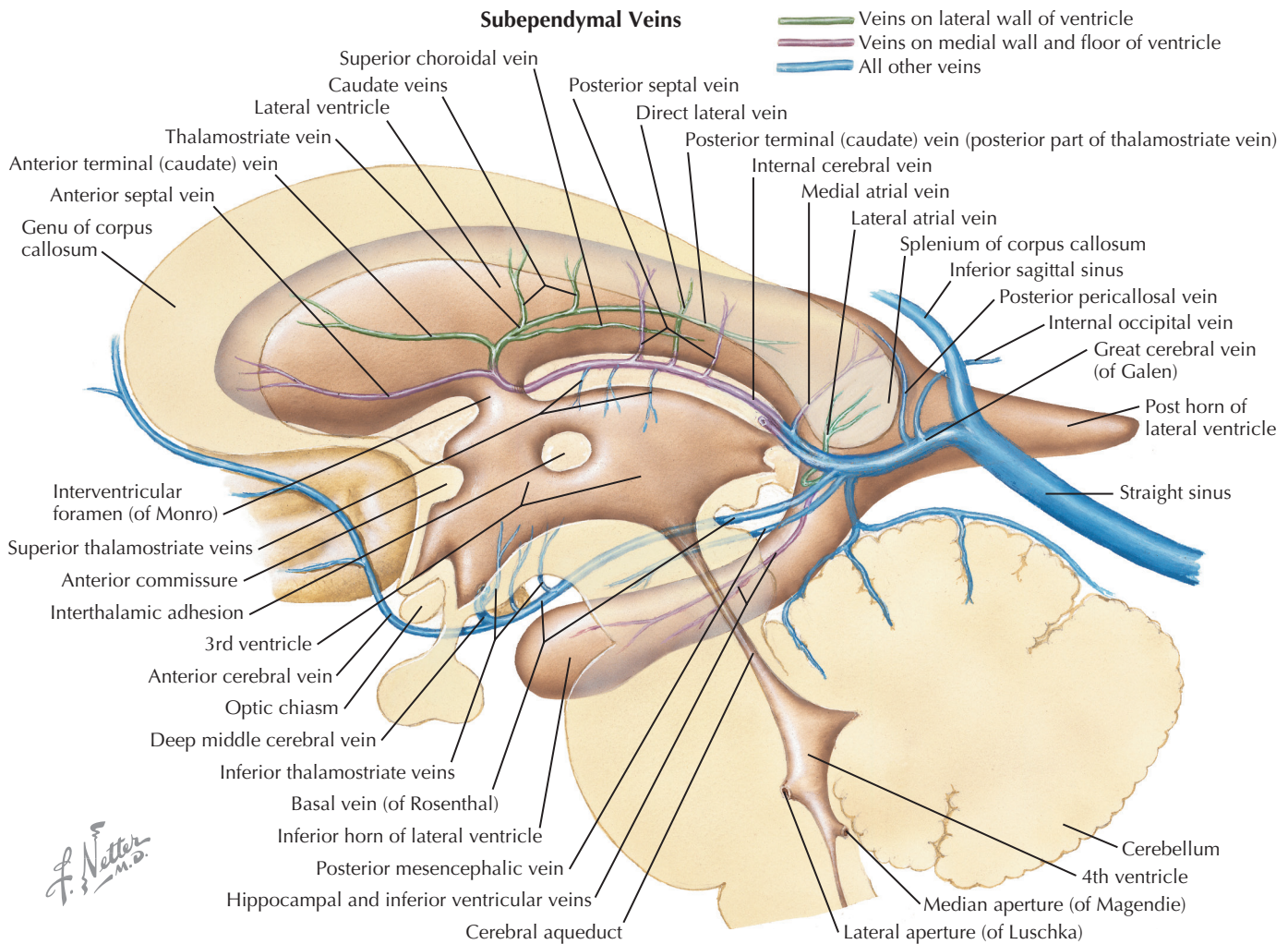
**B. Dissection from Below**

## 7.26 DEEP VENOUS DRAINAGE OF THE BRAIN

**A**, This superior view of the thalamus and basal ganglia reveals the venous drainage of deeper forebrain regions into the posterior venous sinuses. **B**, This basal view of the brain with the

brain stem removed illustrates the drainage of forebrain and mesencephalic venous blood into the great cerebral vein of Galen, heading toward the straight sinus.





### 7.27 DEEP VENOUS DRAINAGE OF THE BRAIN: RELATIONSHIP TO THE VENTRICLES

Subependymal regions of the central nervous system drain venous blood into the inferior sagittal sinus superiorly or into the great cerebral vein of Galen inferiorly, both of which drain into the straight sinus. Occlusion of a vein in this region causes a blockage of drainage and a backup of perfusion, with resultant ischemia of the tissue in the regions of drainage.

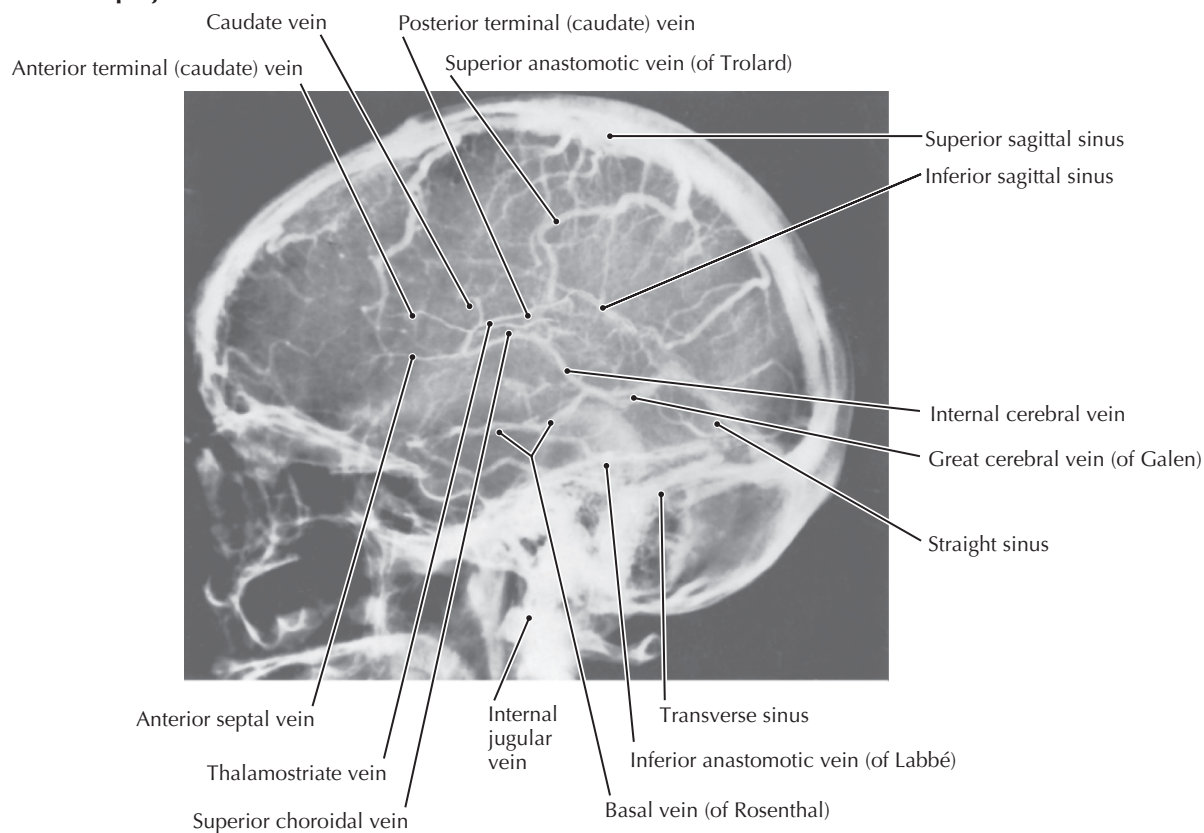
#### CLINICAL POINT

Venous thrombosis can occur following an infectious process, especially in the nearby sinuses, middle ear, or adjacent facial areas. Non-infectious causes of venous thrombosis include dehydration, cancer, polycythemia vera and other hyperviscosity syndromes, inflammatory conditions, and other disorders. The symptoms vary according to the affected focal territory and the spread of the underlying pathological process; they include severe headache, nausea and vomiting, weakness and sensory losses, sometimes aphasia, and sometimes coma.

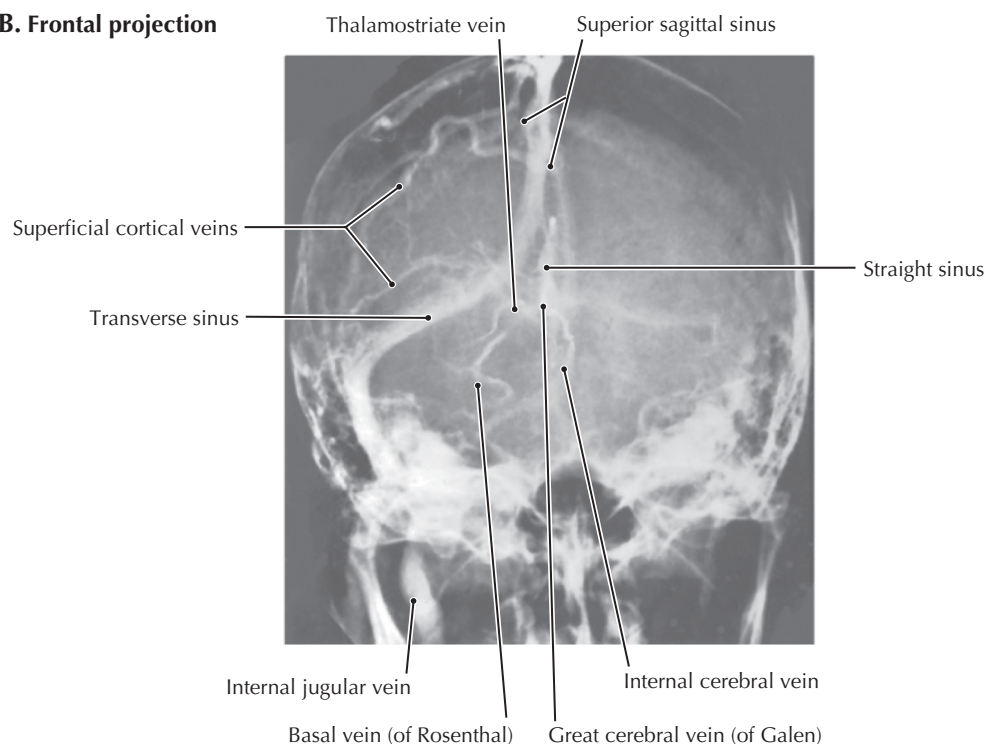


## Subependymal and Superficial Veins Opacified

## A. Lateral projection



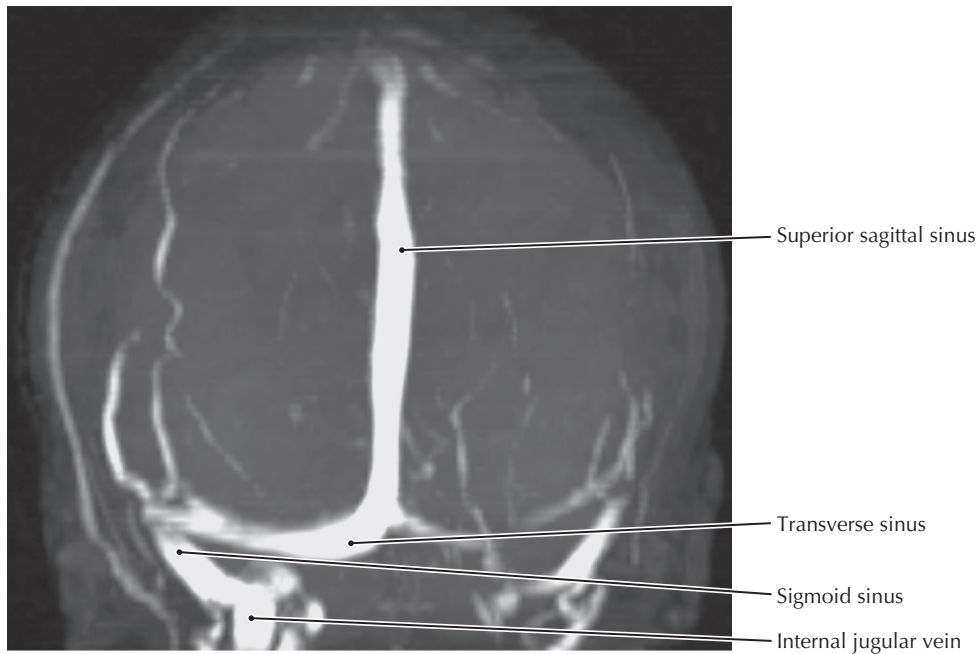
## B. Frontal projection



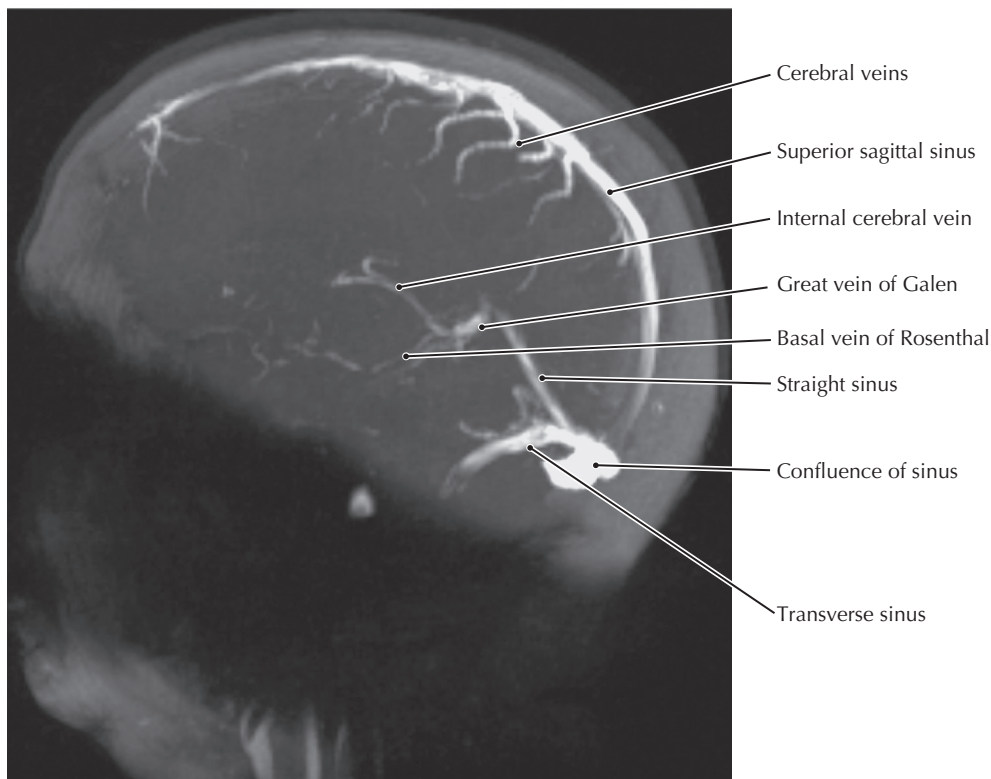
## 7.28 CAROTID VENOGRAMS: VENOUS PHASE

These lateral and anterior venous-phase angiograms illustrate the superior sagittal sinus, the inferior sagittal sinus, and the great cerebral vein of Galen draining into the straight sinus,

the transverse sinus, the basal vein of Rosenthal, and the internal jugular, through which the venous blood of the brain drains back to the heart. See [Video 7-5](#).



A. Coronal view



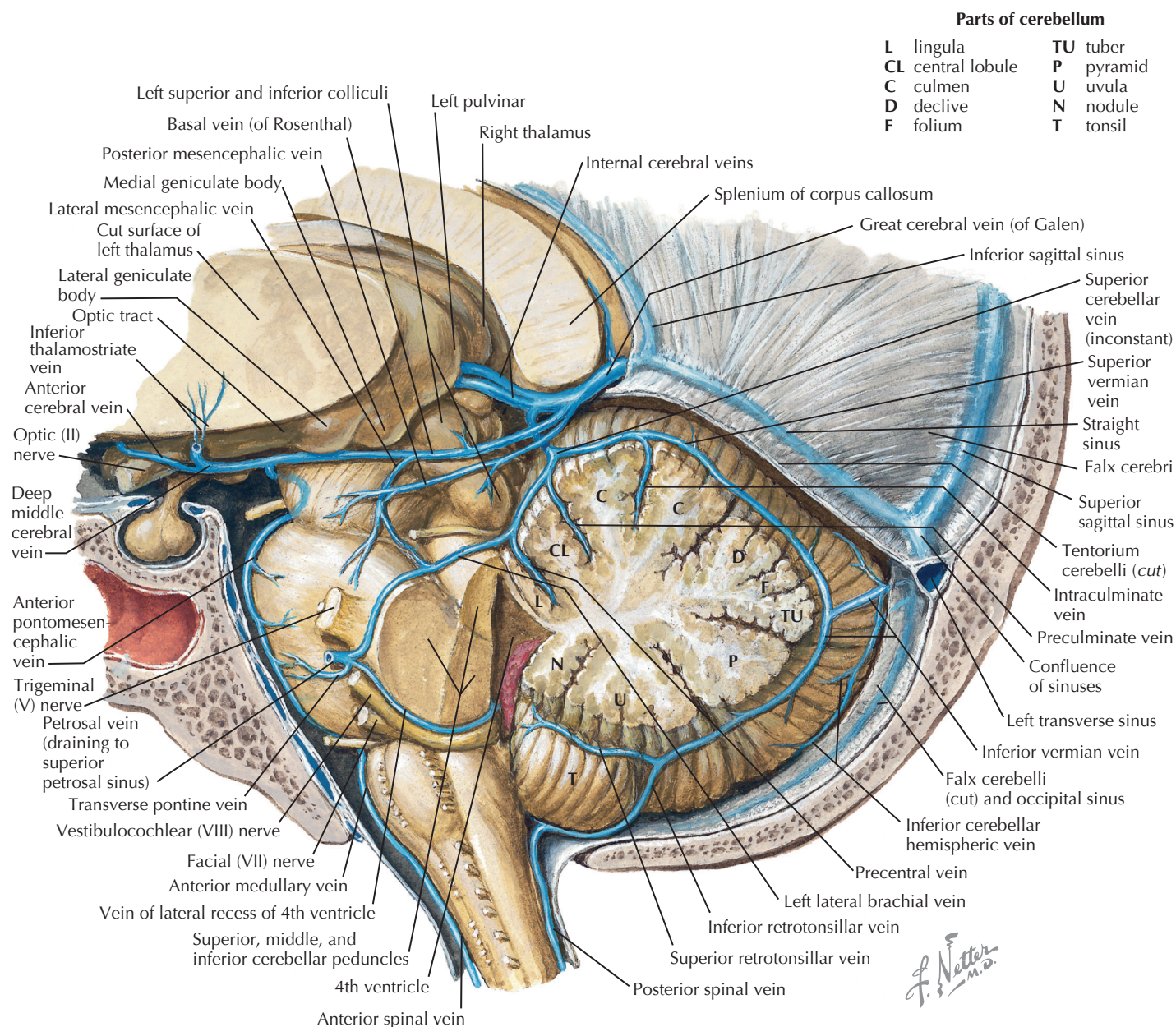
B. Lateral view

### 7.29 MAGNETIC RESONANCE VENOGRAPHY: CORONAL AND SAGITTAL VIEWS

Magnetic resonance venography uses the same principles of flow imaging used in MRA (see Fig. 7.14). The flow of venous blood in the brain is relatively slow and steady compared to the flow of arterial blood. Gradient echo sequences are sensitive to flow but are not sensitive to direction of flow. To distinguish arterial flow from venous flow, a presaturation slab must be applied downstream below the heart or upstream

above the heart prior to placing imaging slices. In a typical magnetic resonance venography of the head, a saturation slab is placed at the level of the carotid bifurcation, and traveling saturation is placed inferiorly to the slice. Multiple two-dimensional thin slices are placed nearly perpendicular to the vessels. **A**, Coronal view. **B**, Sagittal view. These images illustrate the major cerebral veins and sinuses of the brain. See Video 7-6.





### 7.30 VENOUS DRAINAGE OF THE BRAIN STEM AND THE CEREBELLUM

The venous drainage of the cerebellum and the brain stem is anatomically diverse. The veins of the posterior fossa drain the cerebellum and brain stem. The superior group drains the superior cerebellum and upper brain stem posteriorly into the great cerebral vein of Galen and the straight sinus or laterally into the transverse and superior petrosal sinuses. The anterior, or petrosal, group drains the anterior brain stem, the superior and inferior surfaces of the cerebellar hemispheres, and the lateral regions associated with the fourth ventricle into the superior petrosal sinus. The posterior, or tentorial, group drains the inferior portion of the cerebellar vermis and the

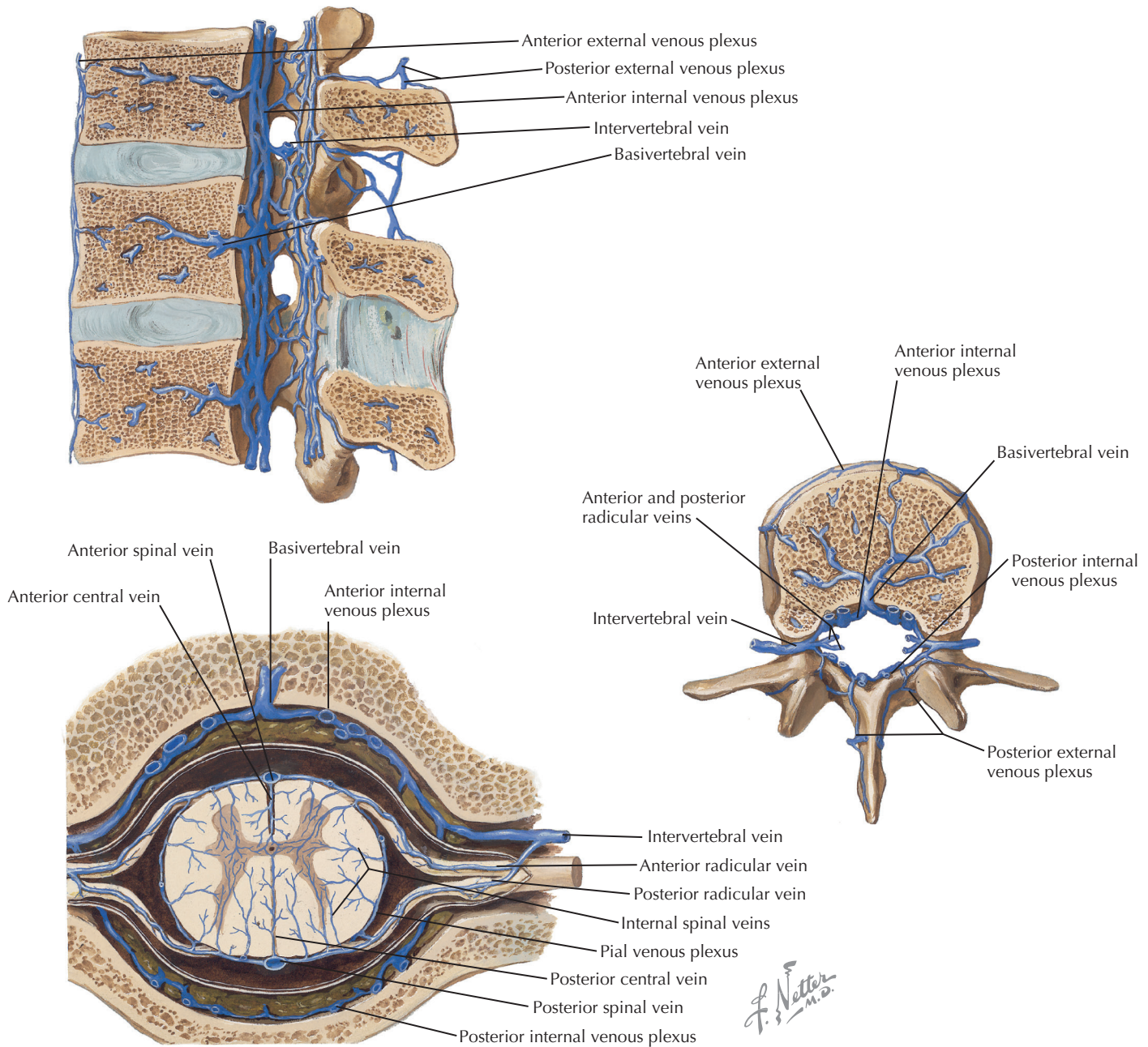
medial portion of the superior and inferior cerebellar hemispheres into the transverse sinus or the straight sinus.

#### CLINICAL POINT

The confluence of sinuses occurs at the junction of the posterior fossa and the occipital lobe. The superior sagittal sinus drains into this confluence of sinuses as the blood flows ultimately toward the jugular vein. The most common sinus thrombosis is that of the superior sagittal sinus. Thrombosis in the posterior portion of this sinus results in headache, increased intracranial pressure with resultant papilledema (after 24 hours), and often a diminished state of consciousness or coma.



## Veins of Spinal Cord and Vertebrae

**7.31 VENOUS DRAINAGE OF THE SPINAL CORD**

An external and internal plexus of veins extends along the entire length of the vertebral column, forming a series of venous rings with extensive anastomoses around each vertebra. Blood from the spinal cord, the vertebrae, and the ligaments drains into these plexuses. Changes in intrathoracic pressure and cerebrospinal fluid pressure can be conveyed through these venous plexuses, affecting the venous volume. Ultimately, these venous plexuses drain through the intervertebral veins into vertebral, posterior intercostals, subcostal, and lumbar and lateral sacral veins.

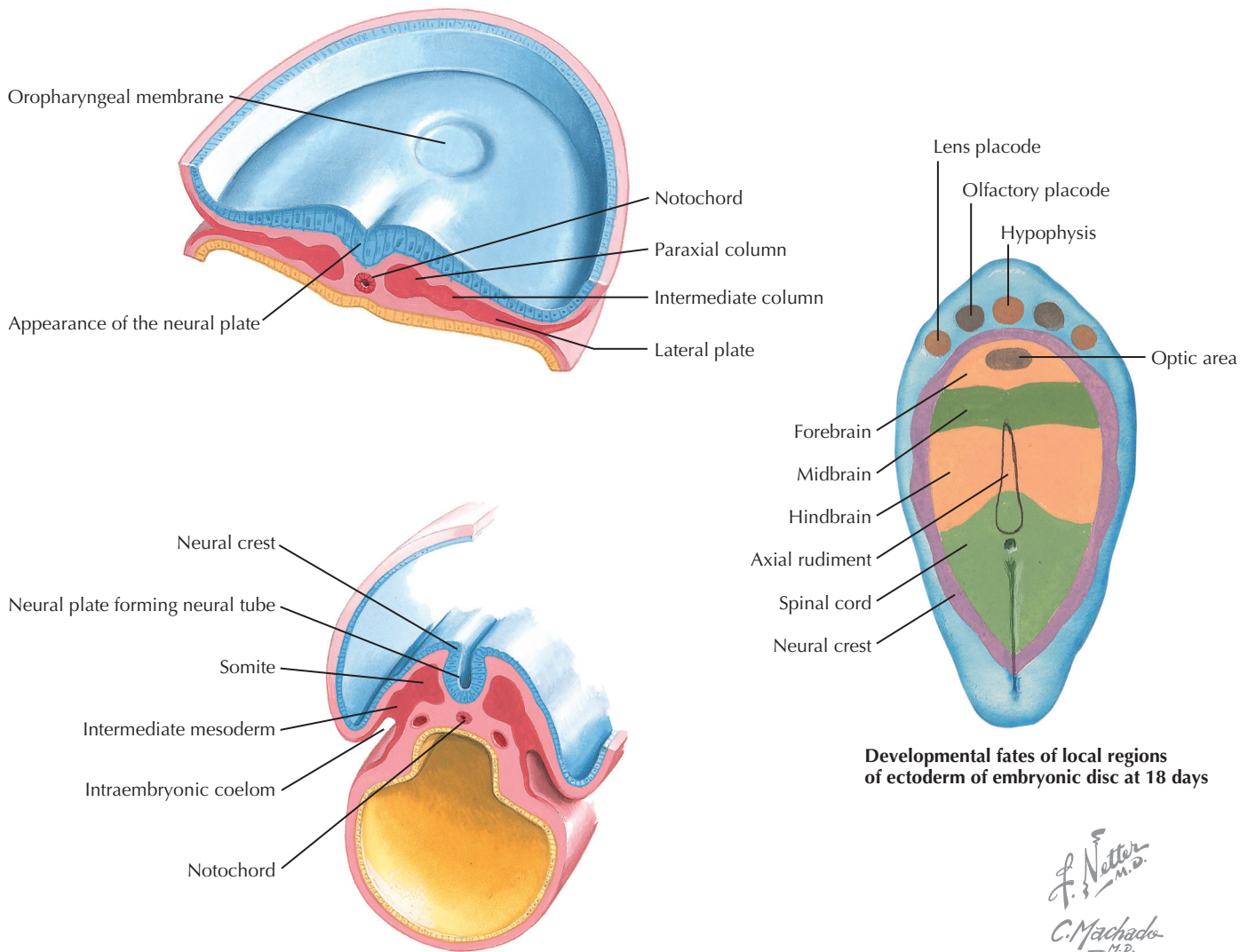
**CLINICAL POINT**

A venous plexus is present in the epidural space surrounding the spinal cord, along with epidural fat. This epidural space is wide enough for the insertion of a catheter and infusion of local anesthesia. The local anesthesia is absorbed into this plexus and diffuses into the adjacent spinal cord, producing profound analgesia at and below the level of the infusion. This technique of epidural anesthesia often is used for analgesia in childbirth and also for a variety of surgeries in which epidural anesthesia is preferable to general anesthesia.

# 8

## DEVELOPMENTAL NEUROSCIENCE

- |             |   |             |   |
|-------------|---|-------------|---|
| <b>8.1</b>  | Formation of the Neural Plate, Neural Tube, and Neural Crest              | <b>8.14</b> | Neurogenesis and Cell Migration in the Developing Neocortex                               |
| <b>8.2</b>  | Neurulation   | <b>8.15</b> | Comparison of 5½ Week and Adult Central Nervous System Regions                            |
| <b>8.3</b>  | Neural Tube Development and Neural Crest Formation                        | <b>8.16</b> | Alar and Basal Plate Derivatives in the Brain Stem  |
| <b>8.4</b>  | Development of Peripheral Axons   | <b>8.17</b> | Adult Derivatives of the Forebrain, Midbrain, and Hindbrain                               |
| <b>8.5</b>  | Somatic Versus Splanchnic Nerve Development                               | <b>8.18</b> | Cranial Nerve Primordia   |
| <b>8.6</b>  | Limb Rotation and Dermatomes  | <b>8.19</b> | Cranial Nerve Neuron Components   |
| <b>8.7</b>  | Neural Proliferation and Differentiation: Walls of the Neural Tube        | <b>8.20</b> | Development of Motor and Preganglionic Autonomic Nuclei in the Brain Stem and Spinal Cord |
| <b>8.8</b>  | Neural Tube and Neural Crest Derivatives                                  | <b>8.21</b> | Development of the Eye and Orbit  |
| <b>8.9</b>  | Early Brain Development: The 28-Day-Old Embryo                            | <b>8.22</b> | Development of the Ear  |
| <b>8.10</b> | Early Brain Development: The 36-Day-Old Embryo                            | <b>8.23</b> | Development of the Pituitary Gland  |
| <b>8.11</b> | Early Brain Development: The 49-Day-Old Embryo and the 3-Month-Old Embryo | <b>8.24</b> | Development of the Ventricles   |
| <b>8.12</b> | Forebrain Development: 7 Weeks through 3 Months                           | <b>8.25</b> | Development of the Fourth Ventricle   |
| <b>8.13</b> | The 6-Month and 9-Month Central Nervous Systems                           | <b>8.26</b> | Neural Tube Defects   |
|             |   | <b>8.27</b> | Defects of the Brain and Skull  |

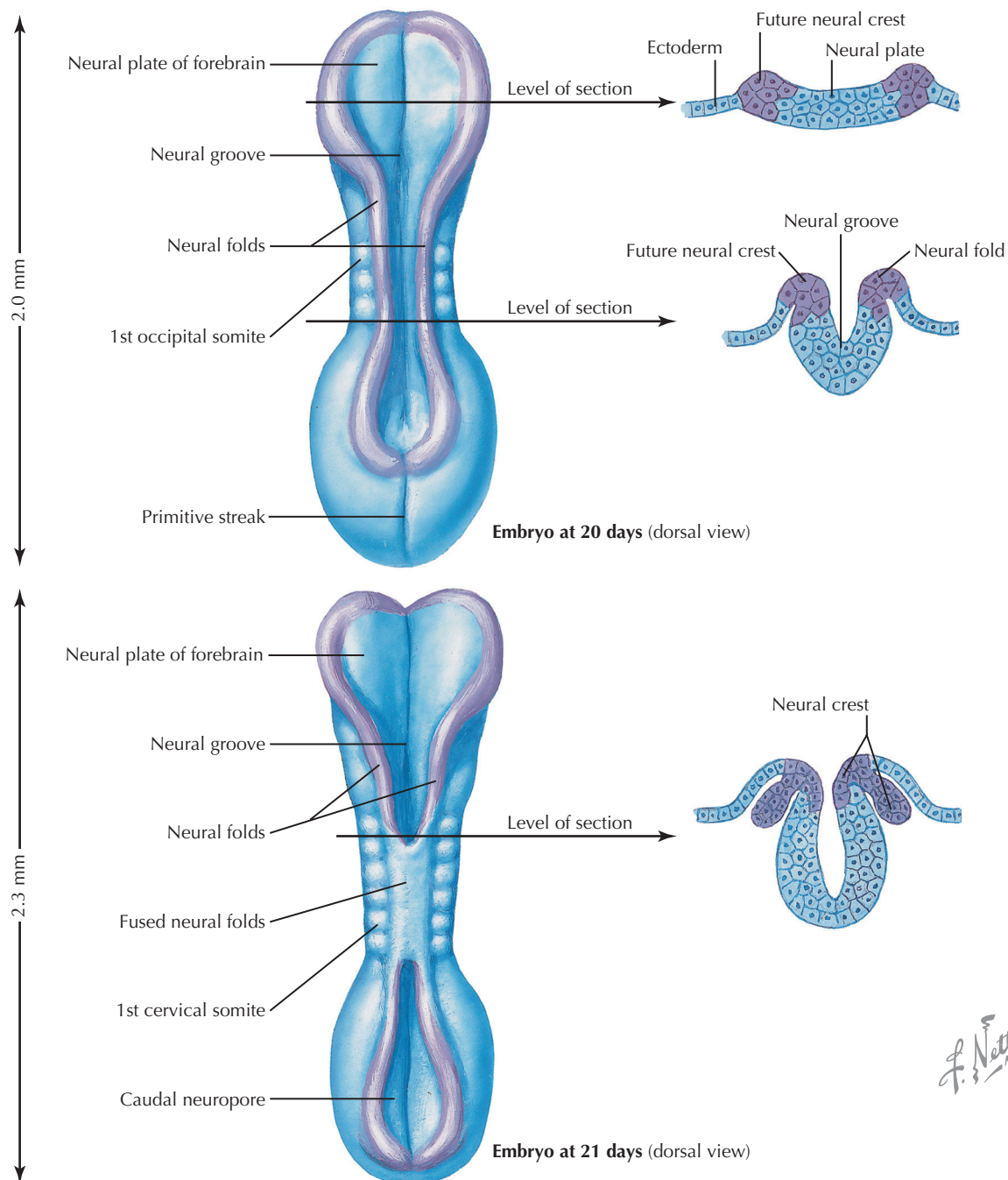


### 8.1 FORMATION OF THE NEURAL PLATE, NEURAL TUBE, AND NEURAL CREST

The neural plate, neural tube, and neural crest form at the 18-day stage of embryonic development. The underlying notochord induces the neural plate, and a midline neural groove forms. The elevated lateral margins become the neural

folds, tissue destined to become the neural crest with future contributions to many components of the peripheral nervous system (PNS). At this very early stage of embryonic development, these neural precursors are vulnerable to toxic insult and other forms of damage.





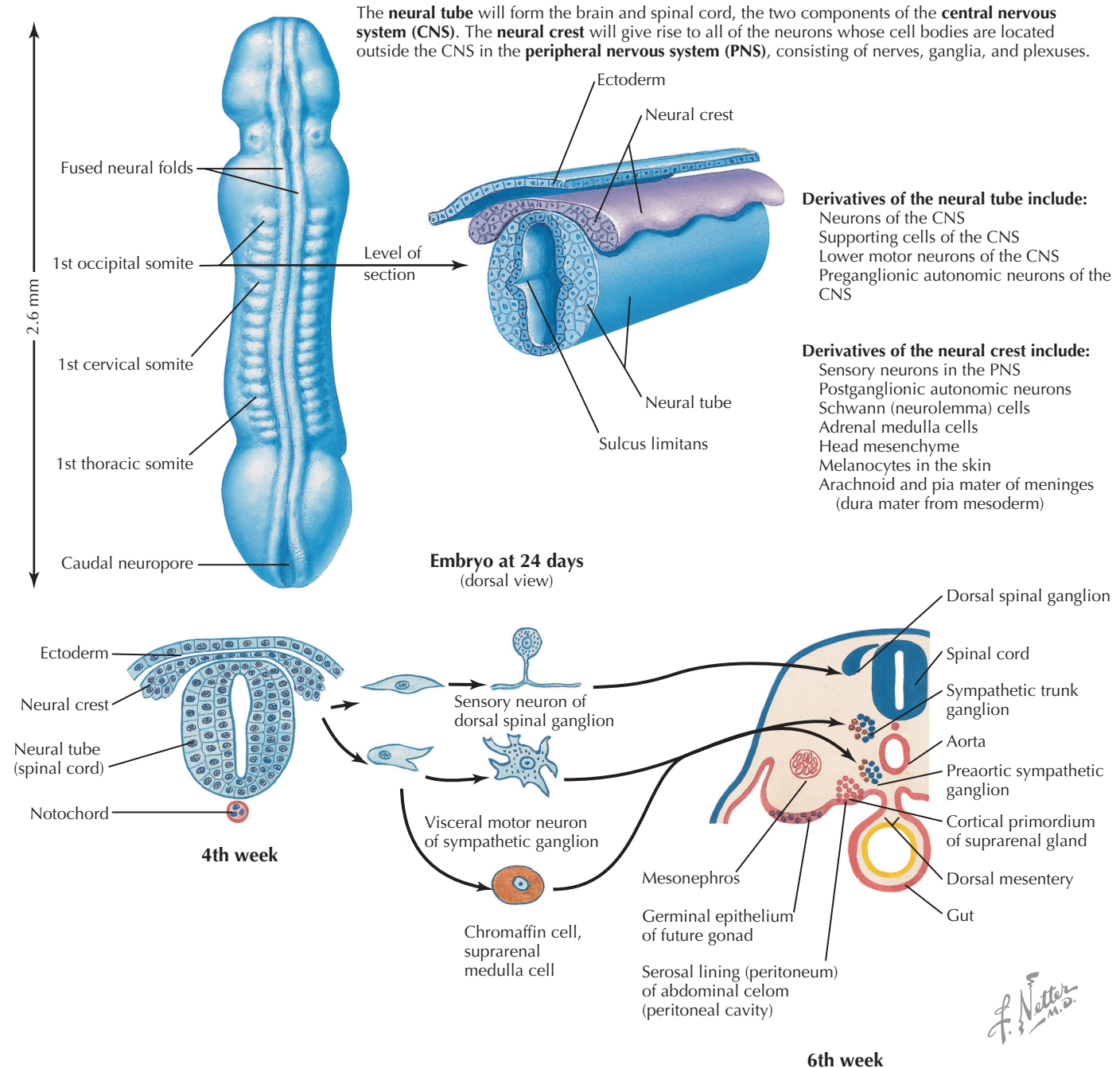
*F. Netter M.D.*

## 8.2 NEURULATION

In the 21- or 22-day-old-embryo, the neural plate, with its midline neural groove, thickens and begins to fold and elevate along either side, allowing the two lateral edges to fuse at the dorsal midline to form the completed neural tube. The central canal, the site of the future development of the ventricular system, is in the center of the neural tube. This process of neurulation continues both caudally and rostrally. Disruption can occur because of failure of full neural tube formation caudally (spina bifida) or rostrally (anencephaly).

### CLINICAL POINT

As the neural plate forms into a neural tube, the process of neurulation results in fused neural folds, starting centrally and moving both caudally and rostrally. Failure of the neural tube to close results in dysraphic defects, with altered development of associated muscles, bone, skin, and meninges. If the anterior neuropore fails to form, anencephaly results, with failure of the brain to develop, accompanied by facial defects. This condition is lethal. Failure of the posterior (caudal) neuropore to close results in spina bifida, with failure of the vertebral arches to fuse. A sacular protrusion from the lumbar region may contain meninges (meningocele) or meninges and spinal cord (meningomyelocele). Meningomyelocele is often accompanied by paraparesis, bowel and bladder dysfunction, sensory disruption at the level of the lesion, motor dysfunction in the lower extremities, and accompanying hydrocephalus or Arnold-Chiari malformation, requiring a ventriculo-peritoneal or ventriculo-jugular shunt.



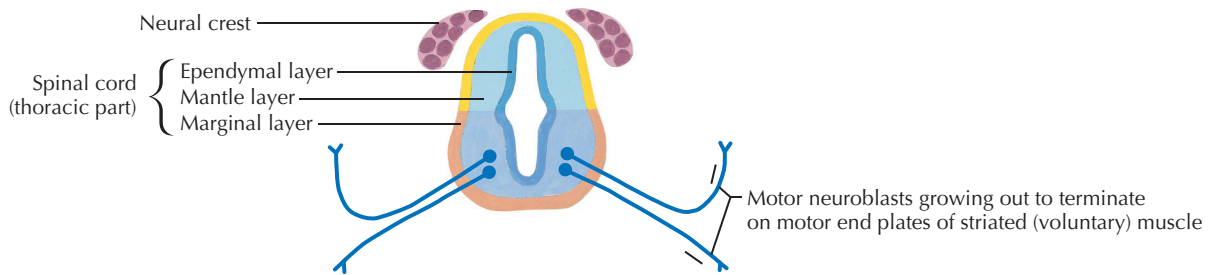
### 8.3 NEURAL TUBE DEVELOPMENT AND NEURAL CREST FORMATION

The dorsal and ventral halves of the neural tube are separated by the sulcus limitans, an external protrusion from the central canal that demarcates the alar plate above from the basal plate below. This important landmark persists at some sites in the adult ventricular system. The alar plate is the source of generation of many neurons with sensory function. The basal plate is the source of generation of many neurons with motor or autonomic function in the spinal cord and the brain stem. The neural crest cells at the edge of the neural folds unite and become a dorsal crest, the neural crest above the neural tube. The neural tube and neural crest separate from the originating ectoderm.

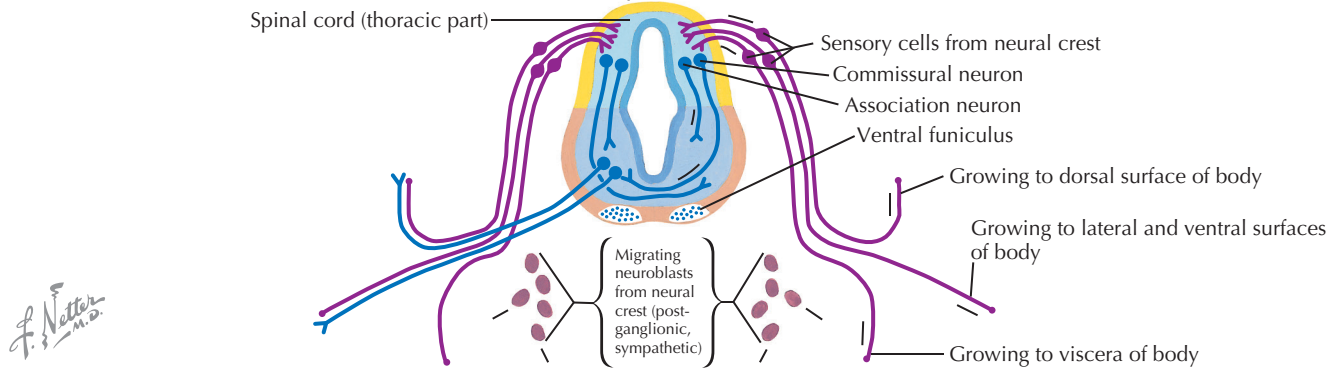
#### CLINICAL POINT

The neural crest gives rise to a wide variety of neural elements of the PNS, including primary sensory neurons, postganglionic autonomic neurons, Schwann cells, adrenal medullary chromaffin cells, pia and arachnoid cells, melanocytes, and some mesenchyme of the head. A failure of the neural crest to develop and migrate properly is seen in Hirschsprung's disease (congenital megacolon), in which sensory signals from the colon are absent, and in familial dysautonomia, in which autonomic symptoms (cardiovascular dysfunction, gastrointestinal dysfunction) and sensory deficits (especially pain and temperature sensation) are present.

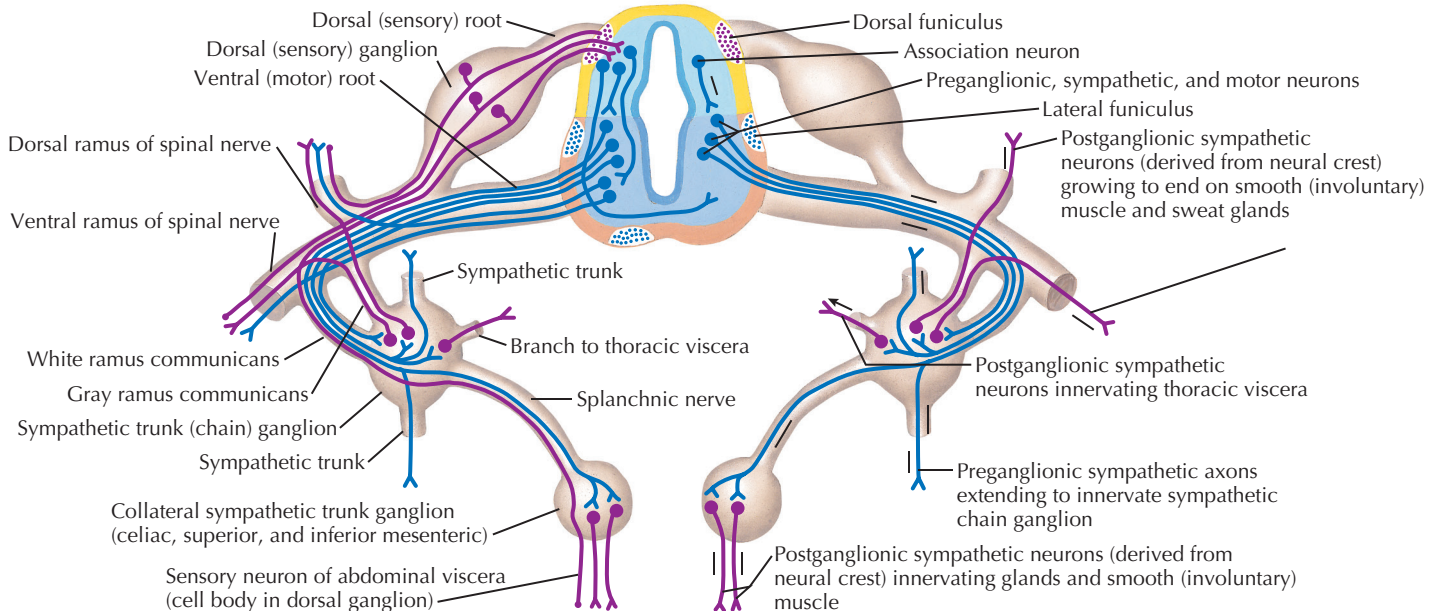
### Differentiation and Growth of Neurons at 26 Days



### Differentiation and Growth of Neurons at 28 Days (right side of diagram shows newly acquired neurons only)



### Differentiation and Growth of Neurons at 5 to 7 Weeks (right side of diagram shows neurons acquired since 28th day only)

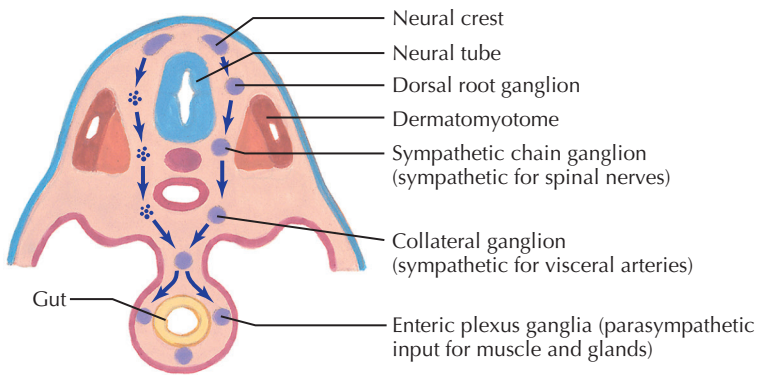


## 8.4 DEVELOPMENT OF PERIPHERAL AXONS

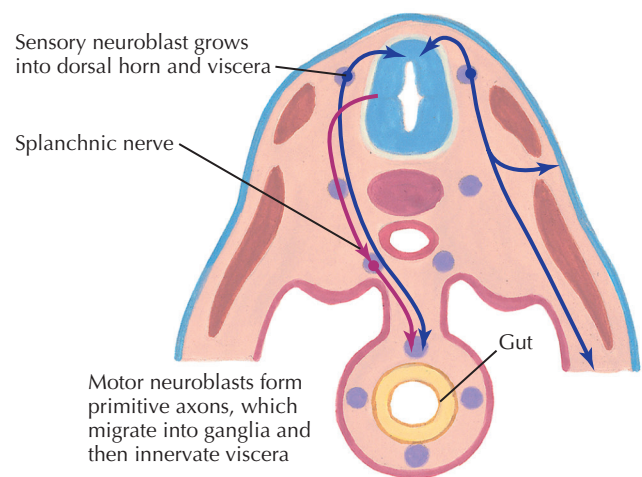
Peripheral axon development is a complex process of central and peripheral neurite extension, trophic and chemotactic factors, and axonal guidance and maintenance by innervated target tissues. Dorsal root ganglion cells are bipolar; a peripheral axonal process is associated with simple or complex sensory receptor cells, and a central axonal process extends into the central nervous system (CNS) to form connections with secondary sensory neurons. The lower motor neurons send motor axons to the developing skeletal muscles through the ventral roots or motor cranial nerves, forming neuromuscular junctions as sites of synaptic connectivity. Motor neurons

that fail to establish such contact with skeletal muscles die. Central preganglionic axons exit in the ventral roots and terminate on sympathetic ganglion cells in the sympathetic chain or collateral ganglia or on parasympathetic intramural ganglia near the organs innervated. Postganglionic axons form connections with target tissues, including smooth muscle, cardiac muscle, secretory glands, some metabolic cells (hepatocytes, fat cells), and cells of the immune system in parenchymal zones of many lymphoid organs. Sensory, motor, and autonomic symptoms can occur in peripheral neuropathies based on disruption of these connections.



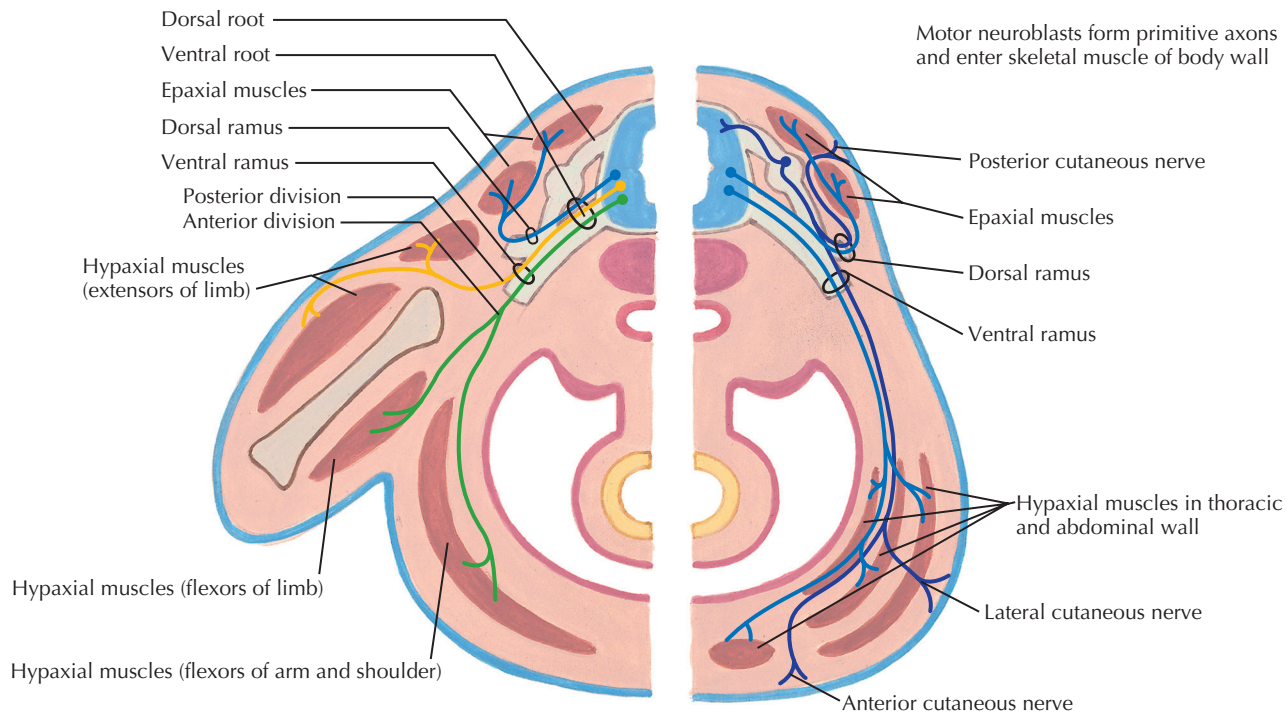


Migration of neural crest cells forms peripheral ganglia of autonomic nervous system



### Autonomic Development

Autonomic nervous system mostly innervates splanchnopleure (viscera)



### Somatic Development

Somatic nervous system innervates somatopleure (body wall)

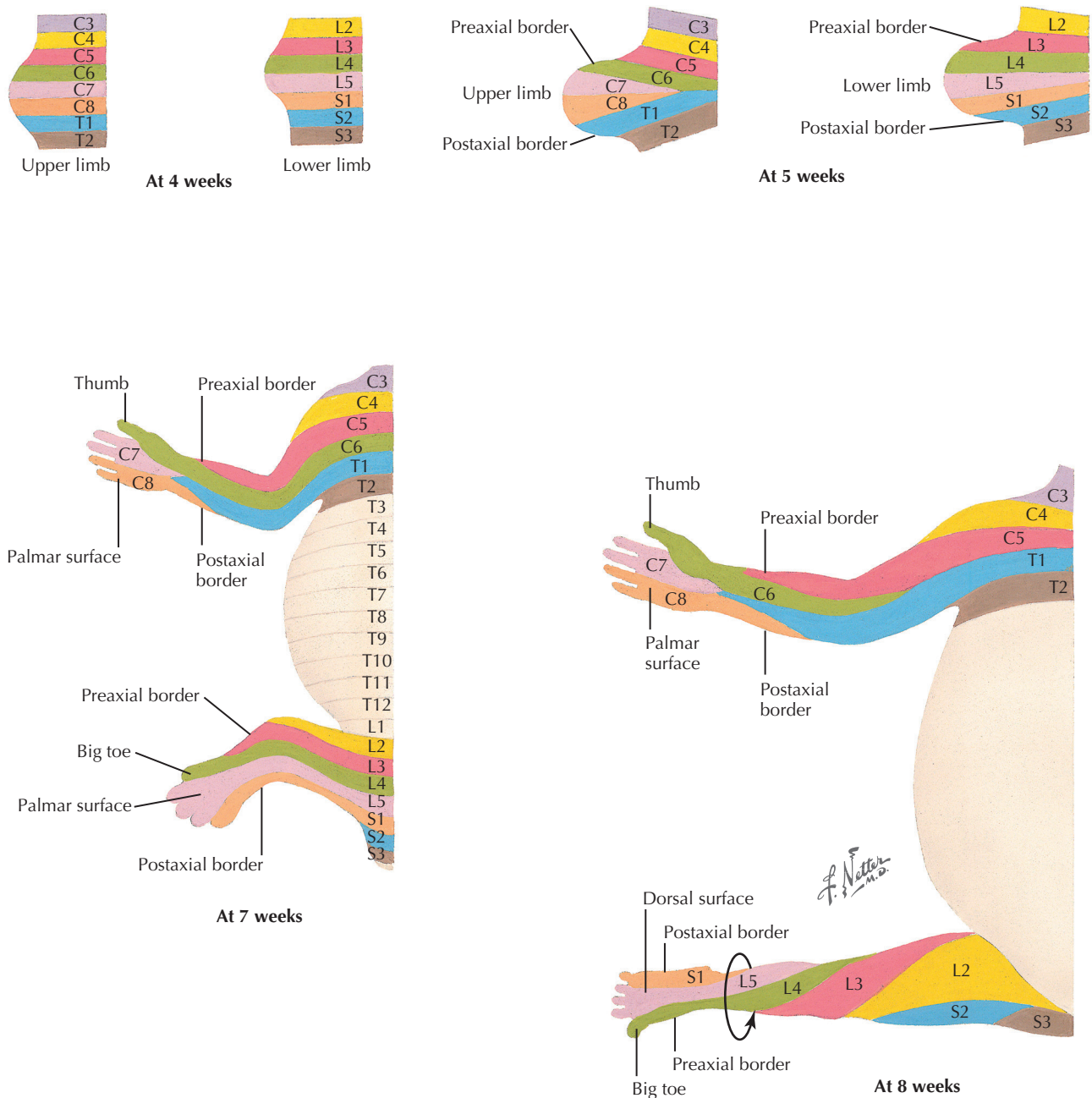
JOHN A. CRAIG, MD

## 8.5 SOMATIC VERSUS SPLANCHNIC NERVE DEVELOPMENT

Somatopleure and splanchnopleure constitute the embryonic basis for the subdivision of the PNS into spinal (somatic) nerves and splanchnic (autonomic) nerves. The somatopleure develops from ectoderm and the somatic portion of lateral plate mesoderm. Somite hypoblasts migrate into somatopleure to form the lateral and ventral aspects of the body wall,

including the limbs. Splanchnopleure, derived from endoderm and lateral plate mesoderm, give rise to visceral organs. The ventral rami migrate into somatopleure, and splanchnic nerves grow into splanchnopleure. Thoracic and lumbar splanchnic nerves have sympathetic and visceral sensory axonal components. Pelvic splanchnic nerves (S2–S4) have parasympathetic and visceral sensory axonal components.

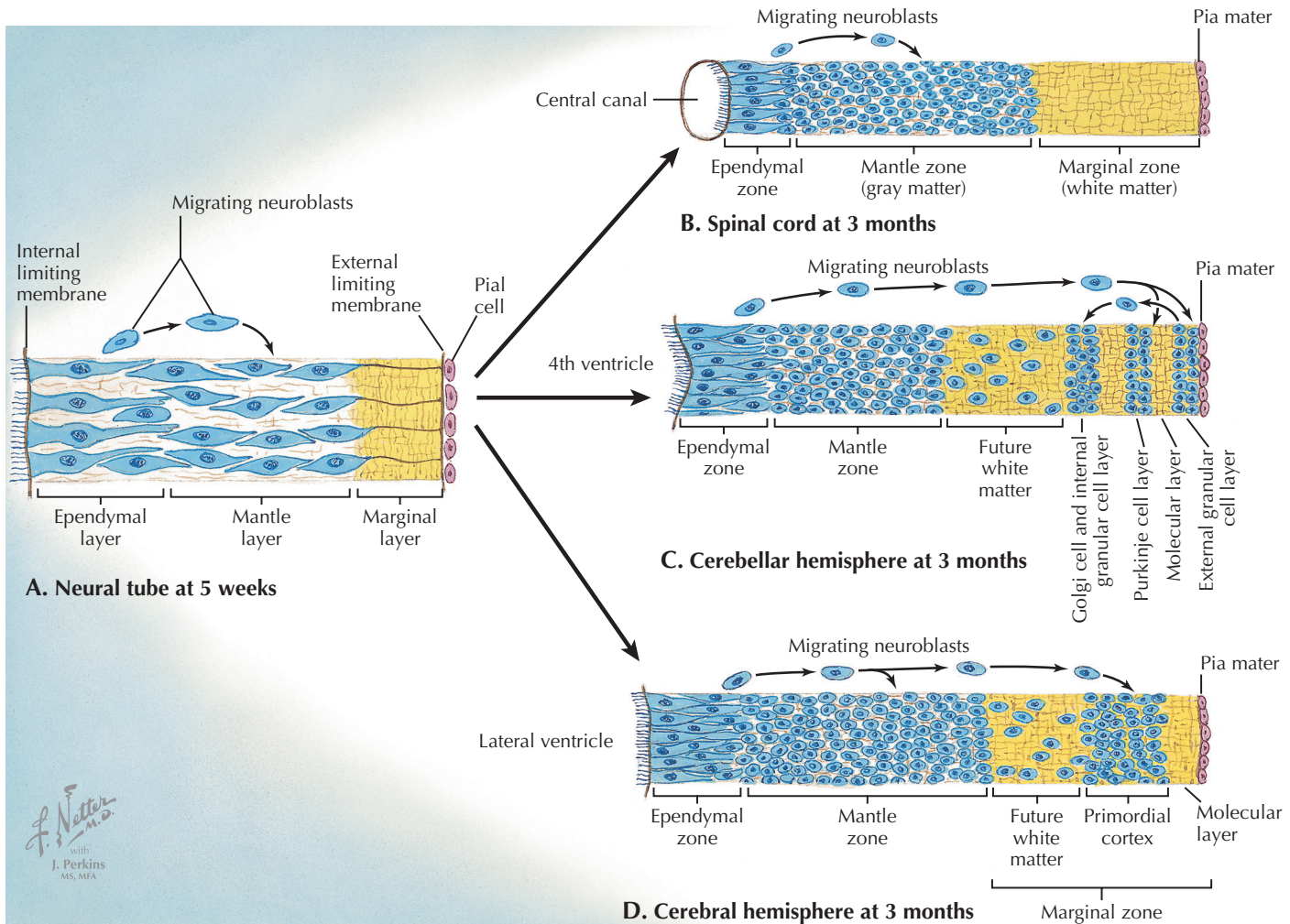
### Changes in ventral dermatome pattern (cutaneous sensory nerve distribution) during limb development



## 8.6 LIMB ROTATION AND DERMATOMES

Rotation of the lower limb results in a reversal of the preaxial and postaxial borders, producing a spiral arrangement of dermatomes. Spinal nerve segments on the anterior surface of the lower extremity extend medially and inferiorly; the great toe (hallux) is supplied by nerves from a more rostral dermatome

(L4) than the little toe (S1). The lower extremity is an extension of the trunk, and the most caudal dermatomes (sacral and coccygeal) supply the perineum, not the foot. Cervical dermatomes maintain a relatively orderly distribution to the upper extremity with minimal rotation.

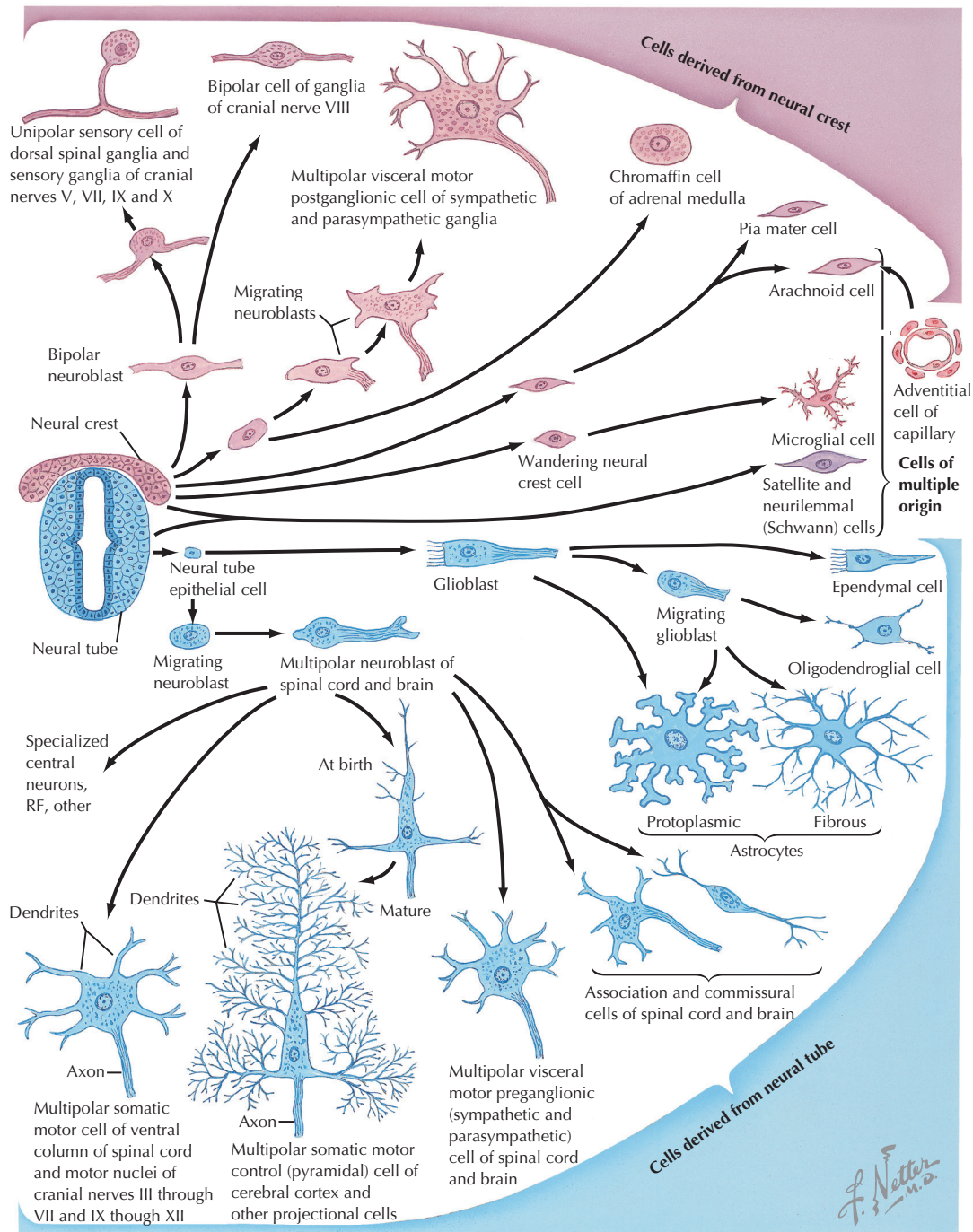


## 8.7 NEURAL PROLIFERATION AND DIFFERENTIATION: WALLS OF THE NEURAL TUBE

Early in development (5 weeks), neuroblasts in the ependymal layer lining the central canal move back and forth from the ependymal surface to the pial surface, replicating as they go. Neural migration follows distinctive patterns in different regions of the neural tube. In the spinal cord, neurons migrate into the inner mantle zone, leaving the outer marginal zone as a site for axonal pathways. In the cerebellar cortex, some

neurons migrate to an outer location on the outer pial surface as an external granular layer, from which granular cells then migrate inward to synapse with other neurons present in deeper layers of the cerebellar cortex. In the cerebral cortex, neurons migrate to the outer zone, where the gray matter (neuronal cell bodies) remains on the surface, external to the white matter (nerve fibers). These developmental patterns reflect the anatomical organization of the mature structures, their blood supply, and their vulnerability to injury by tumors, vascular insults, trauma, and other disorders.



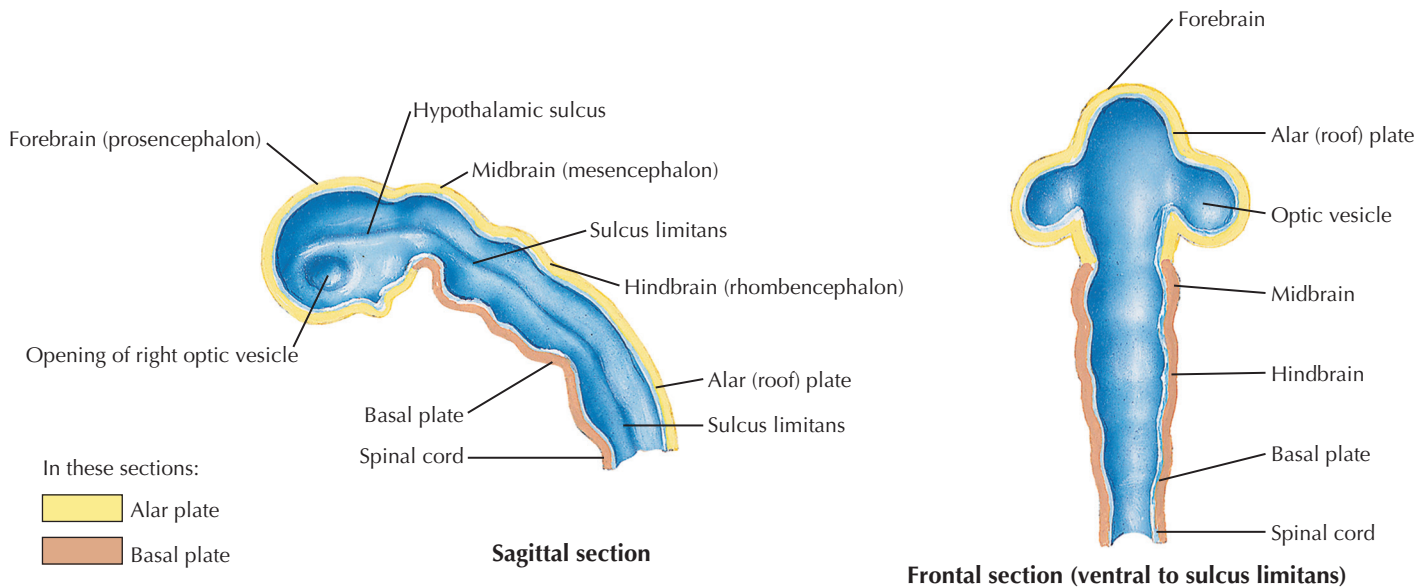
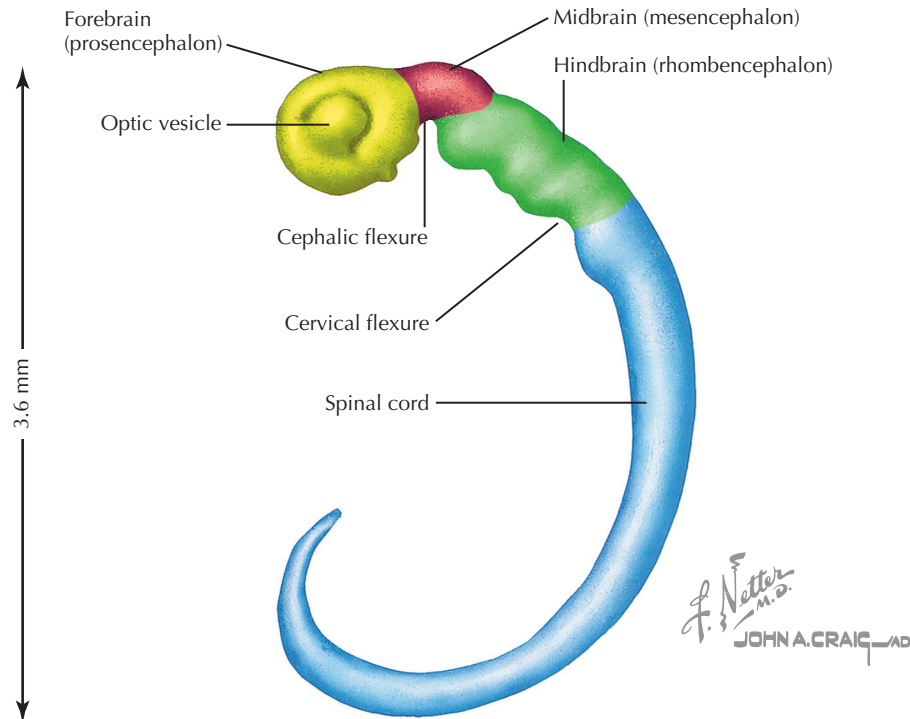


## 8.8 NEURAL TUBE AND NEURAL CREST DERIVATIVES

Neural tube ependymal cells give rise to neuroblasts, from which the neurons of the CNS are derived. They also give rise to the glioblasts, from which the mature ependymal cells, astrocytes, and oligodendroglia are derived. Microglia, the “scavenger cells” of the CNS, are derived mainly from mesodermal precursors. Cells of glial origin are the predominant cells that give rise to CNS tumors. The neural crest cells give rise to many peripheral neural structures, including

primary sensory neurons, postganglionic autonomic neurons of both the sympathetic and parasympathetic systems, adrenal medullary chromaffin cells, and pial and arachnoid cells, Schwann cells (the supporting cells of the PNS), and some other specialized cell types. Neural crest cells can be damaged selectively in some disorders (e.g., familial dysautonomias) and also can give rise to specific tumor cell types such as pheochromocytomas. Most microglial cells are derived from specialized mesenchymal cells infiltrating from the yolk sac.

## Central nervous system at 28 days



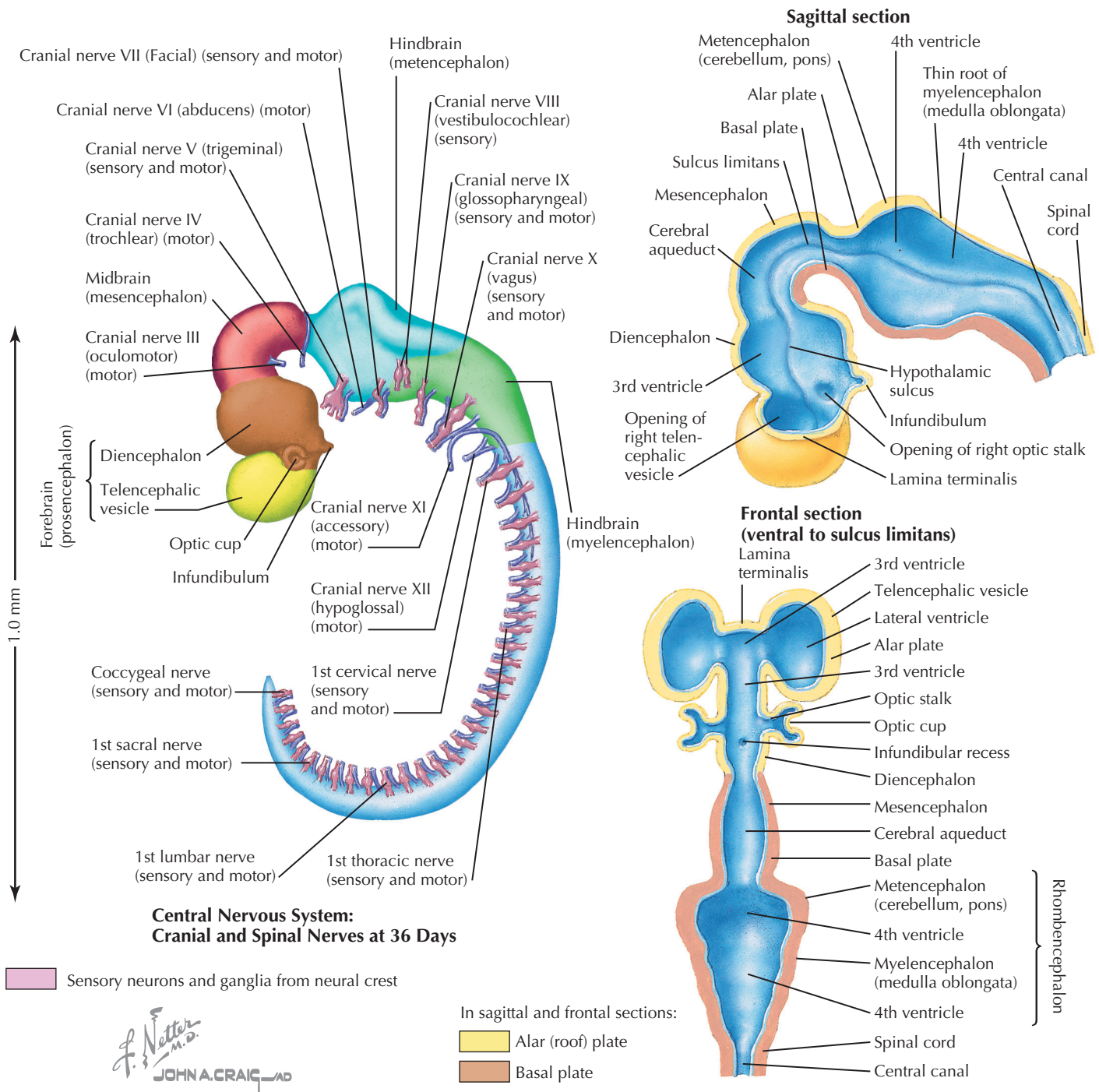
### 8.9 EARLY BRAIN DEVELOPMENT: THE 28-DAY-OLD EMBRYO

Some components of the neural tube expand differentially, resulting in bends or flexures that separate the neural tube into caudal to rostral components. The cervical flexure caudally and the cephalic flexure rostrally result from the differential expansion. Three regions of rapid cellular proliferation develop: the forebrain (prosencephalon) rostrally; the mesencephalon (midbrain) in the middle; and the hindbrain (rhombencephalon) caudally. The ventricular system bends and expands to accommodate the increasing neural growth. An outgrowth from the caudal part of the prosencephalon

extends from the future diencephalon to become the optic cup, giving rise to the future retina and its central connections.

#### CLINICAL POINT

The optic vesicle develops from the prosencephalon, specifically the future diencephalon. As a consequence, the neuroretina is actually a central neural derivative and not a peripheral neural crest derivative. Therefore, the retina is supplied with CNS vasculature, and the ganglion cells of the retina (projecting into the optic nerve, chiasm, and tract) are actually CNS axons myelinated by oligodendroglia and surrounded by subarachnoid space and its cerebrospinal fluid. As a CNS tract, the optic nerve is subject to central demyelinating lesions as seen in multiple sclerosis. The retinal vasculature is the only CNS vasculature that is directly observable by ophthalmoscopy.

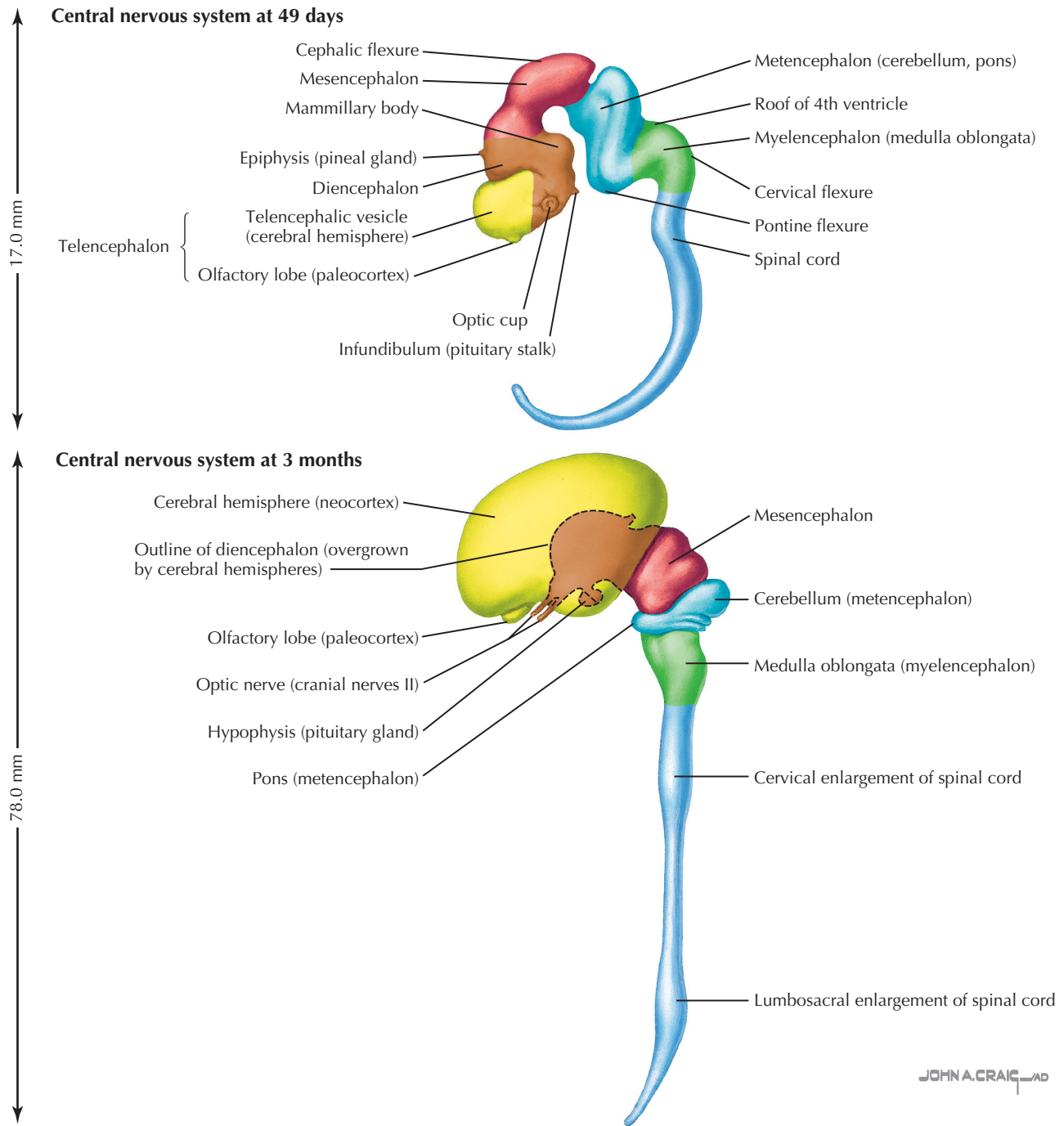


### 8.10 EARLY BRAIN DEVELOPMENT: THE 36-DAY-OLD EMBRYO

By day 36, the prosencephalon begins to expand rapidly as the future diencephalon (thalamus and hypothalamus) and telencephalon (basal ganglia, limbic forebrain, olfactory system, and cerebral cortex). This rapid growth is accompanied by the formation of the thin third ventricle for the diencephalon and the C-shaped lateral ventricles from the rostral end of the

original central canal for the telencephalon. The rhombencephalon further develops into two distinct regions, the metencephalon (future pons and cerebellum) and the myelencephalon (future medulla). Distinct spinal nerves and cranial nerves begin to form as sensory and motor neurons differentiate and begin to connect with their appropriate targets in the periphery.





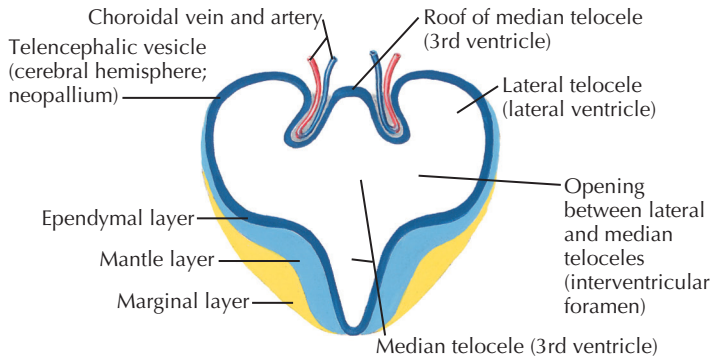
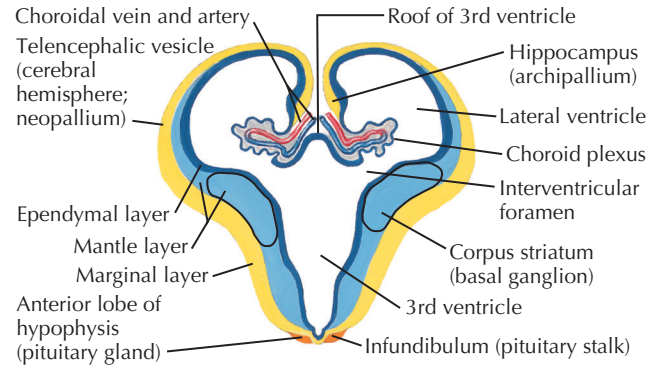
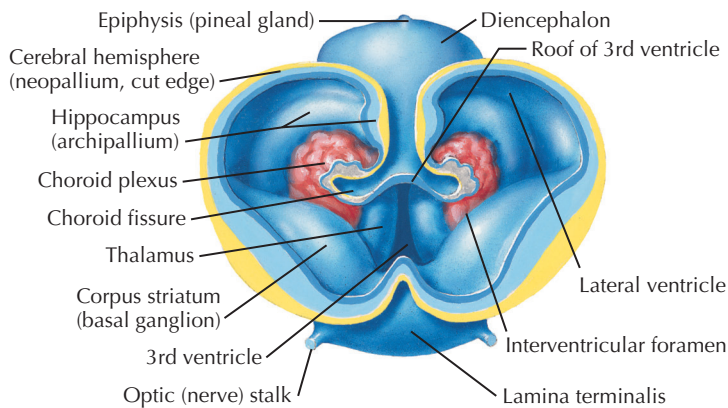
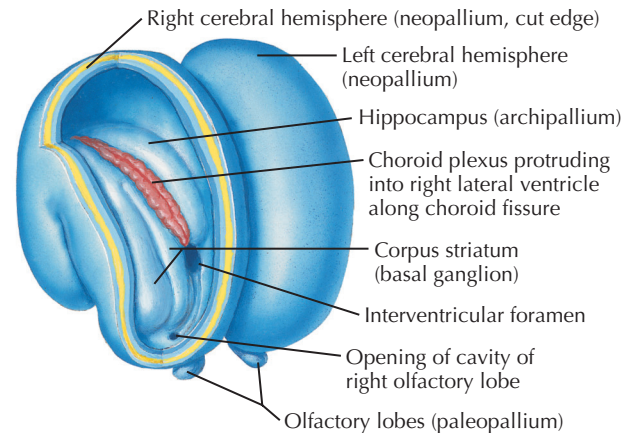
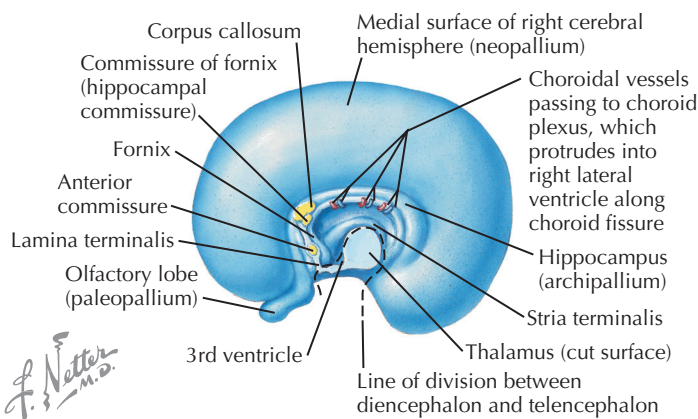
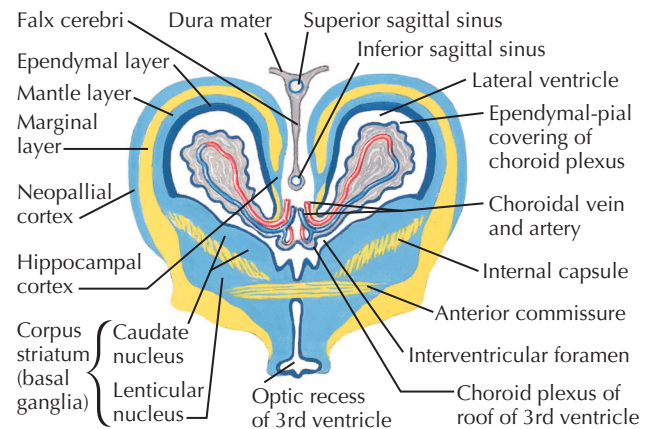
### 8.11 EARLY BRAIN DEVELOPMENT: THE 49-DAY-OLD EMBRYO AND THE 3-MONTH-OLD EMBRYO

By 49 days of age, the diencephalons and telencephalon differentiate into distinct components: the thalamus dorsally and the hypothalamus ventrally from the diencephalons, and the olfactory lobe, basal ganglia, limbic forebrain structures, and cerebral cortex from the telencephalon. The metencephalon (pons) and myelencephalon (medulla) develop further and fold, separated by the pontine flexure. Between 49 days and 3 months, massive development of the telencephalon overrides and covers the diencephalon. The cerebellum forms from the rhombic lips of the metencephalon as neurons travel dorsally to overlie the future pons and eventually most of the brain

stem. The mesencephalon expands dorsally, forming the superior and inferior colliculi (quadrigenal bodies). The continuing growth of the spinal cord as it connects with peripheral tissues in the developing limbs forms the cervical and lumbosacral enlargements.

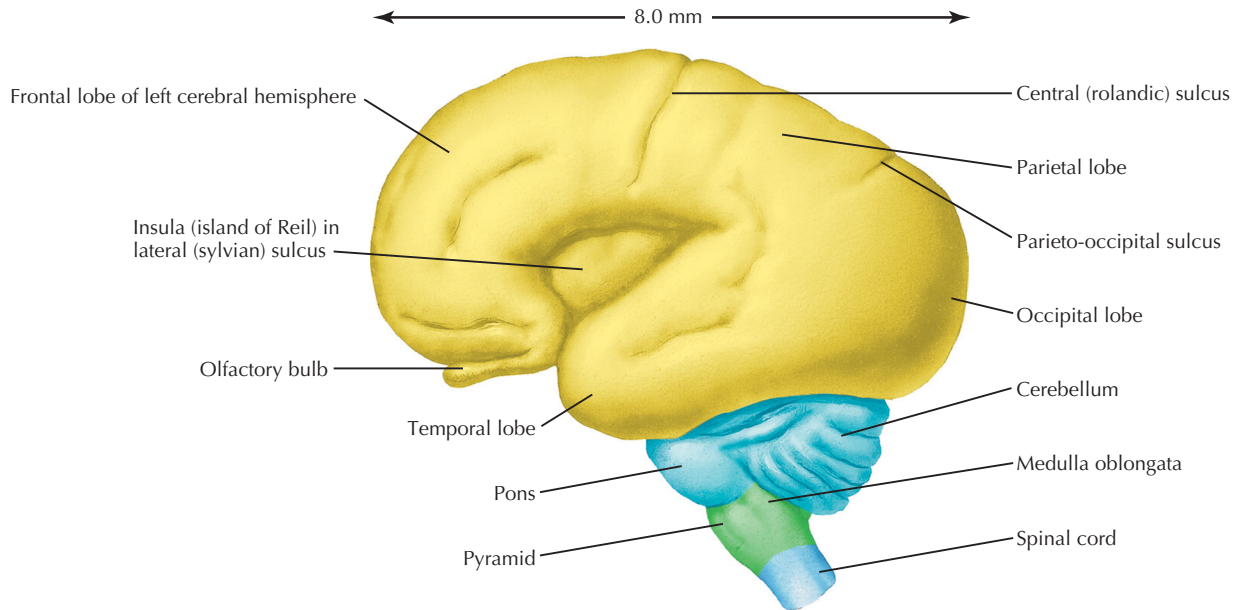
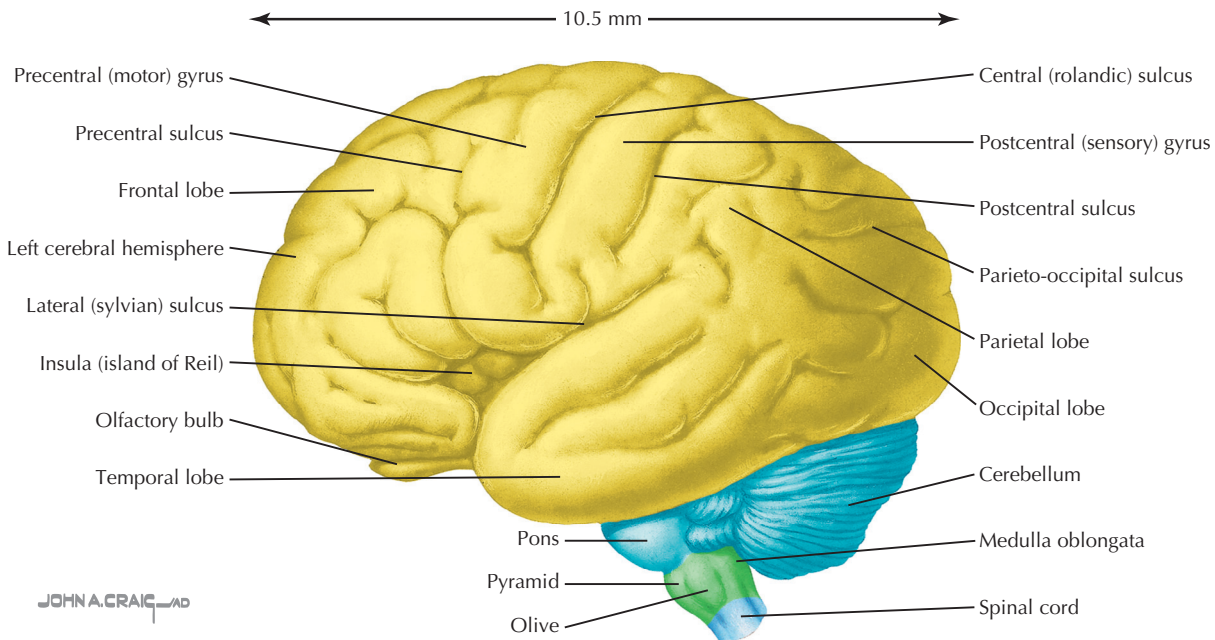
#### CLINICAL POINT

The process by which the prosencephalon gives rise to the diencephalons and telencephalon is termed prosencephalization. A failure of this process to form the two hemispheres results in holoprosencephaly, with a single large forebrain ventricle, a poorly developed diencephalon, and aberrant development of telencephalic structures. This severe defect in forebrain formation is also accompanied by severe facial malformations.

**Forebrain at 7 Weeks** (transverse section)**Telencephalon at 7½ Weeks** (transverse section)**Forebrain at 2 Months** (coronal section; anterior view)**Telencephalon at 2½ Months** (right anterior view)**Right Cerebral Hemisphere at 3 Months** (medial aspect)**Cerebral Hemispheres at 3 Months** (coronal section)**8.12 FOREBRAIN DEVELOPMENT: 7 WEEKS THROUGH 3 MONTHS**

Neurons of the developing telencephalon move rostrally, dorsally, and then around the diencephalon in a C shape toward the anterior pole of the temporal lobe. The hippocampal formation forms in a dorsal and anterior position and migrates in a C-shaped course into the anterior temporal lobe. The amygdala develops in a similar manner, giving rise to the stria terminalis pathway in a C shape. The lateral ventricles follow the same C-shaped developmental process anatomically. The

caudate nucleus also extends around the telencephalon in a C-shaped pattern, with the large head of the nucleus remaining anterior and the much smaller body and tail following as a thinner C-shaped structure that ends ventrally in the temporal horn of the lateral ventricle. The corpus callosum and anterior commissure connect the two hemispheres. The internal capsule funnels centrally in the core of the forebrain on either side; the posterior limb continues caudally as the cerebral peduncle.

**Brain at 6 months****Brain at 9 months (birth)****8.13 THE 6-MONTH AND 9-MONTH CENTRAL NERVOUS SYSTEMS**

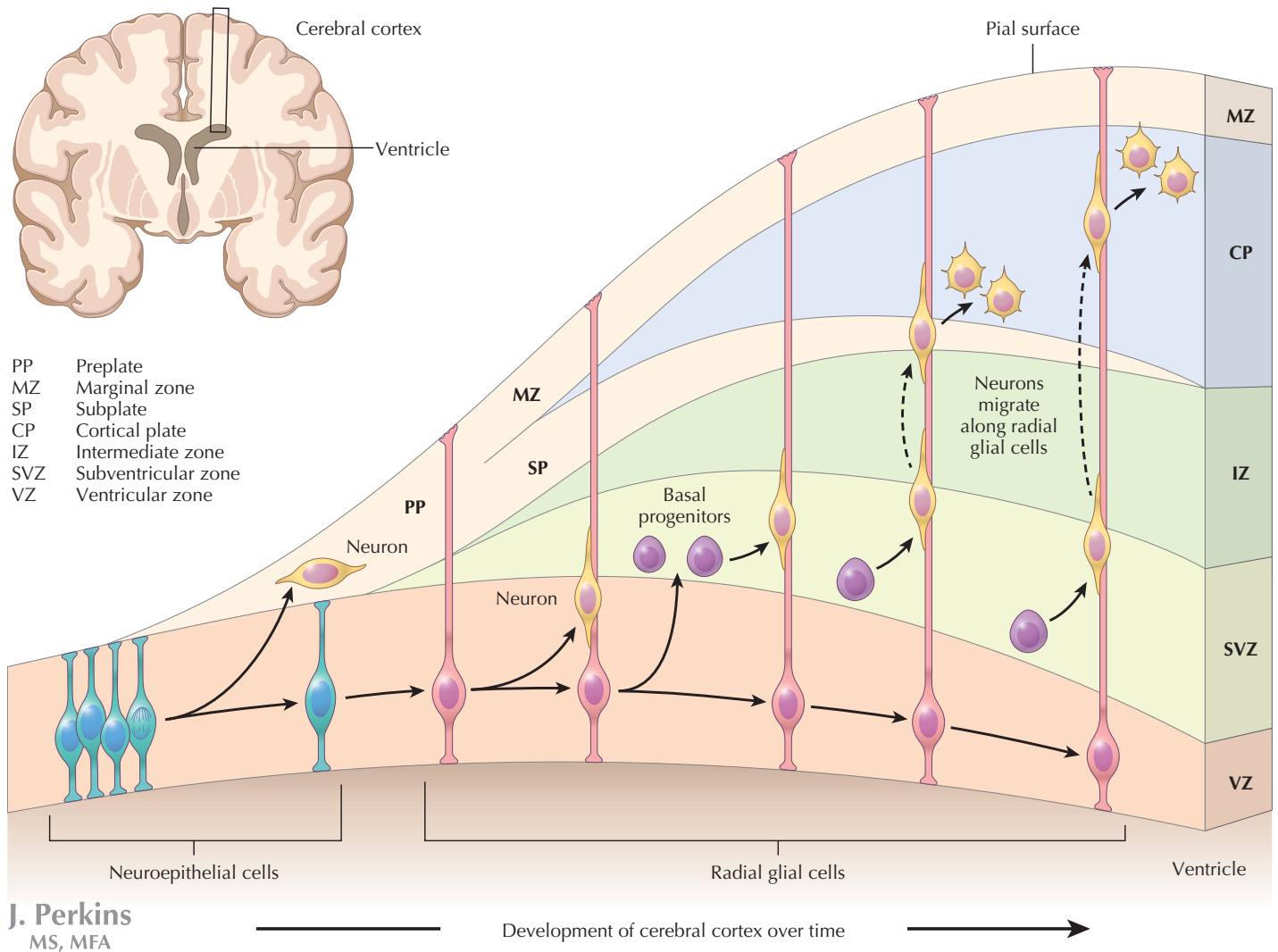
At 6 months, the brain stem has differentiated into the medulla, pons, and midbrain, with the developing cerebellum overlying them dorsally. Even though the diencephalon is rapidly developing, the overlying telencephalon shows massive growth rostrally, then caudally, downward, and forward into the temporal lobe. From 6 to 9 months of age, the cerebral cortex forms its characteristic convolutions with gyri and sulci, and the cerebellar cortex forms its distinctive folds, the folia. Within the forebrain, the major components of the basal ganglia, the limbic forebrain structures (i.e., the amygdala and hippocampal formation), the olfactory system, and the cerebral cortex develop rapidly. Most neurons are present at birth; some populations of granular cells in the cerebellum, the dentate gyrus

of the hippocampus, and the cerebral cortex, form postnatally in response to environmental stimuli. The in utero and postnatal environments provide major influences on neural development and function.

**CLINICAL POINT**

The cerebral cortex develops through an orderly process of cell proliferation from the ventricular zone and then the subventricular zone, with proper cell migration and interconnectivity extending through prenatal life and well into postnatal life. A failure of proper cell proliferation and migration of cortical neurons can result in the failure of proper formation of gyri and sulci, giving a smooth cortical surface appearance called lissencephaly. In some situations, gyri can be unusually small (microgyria) or unusually large (pachygyria). These developmental defects may be accompanied by profound neural deficits and retardation.

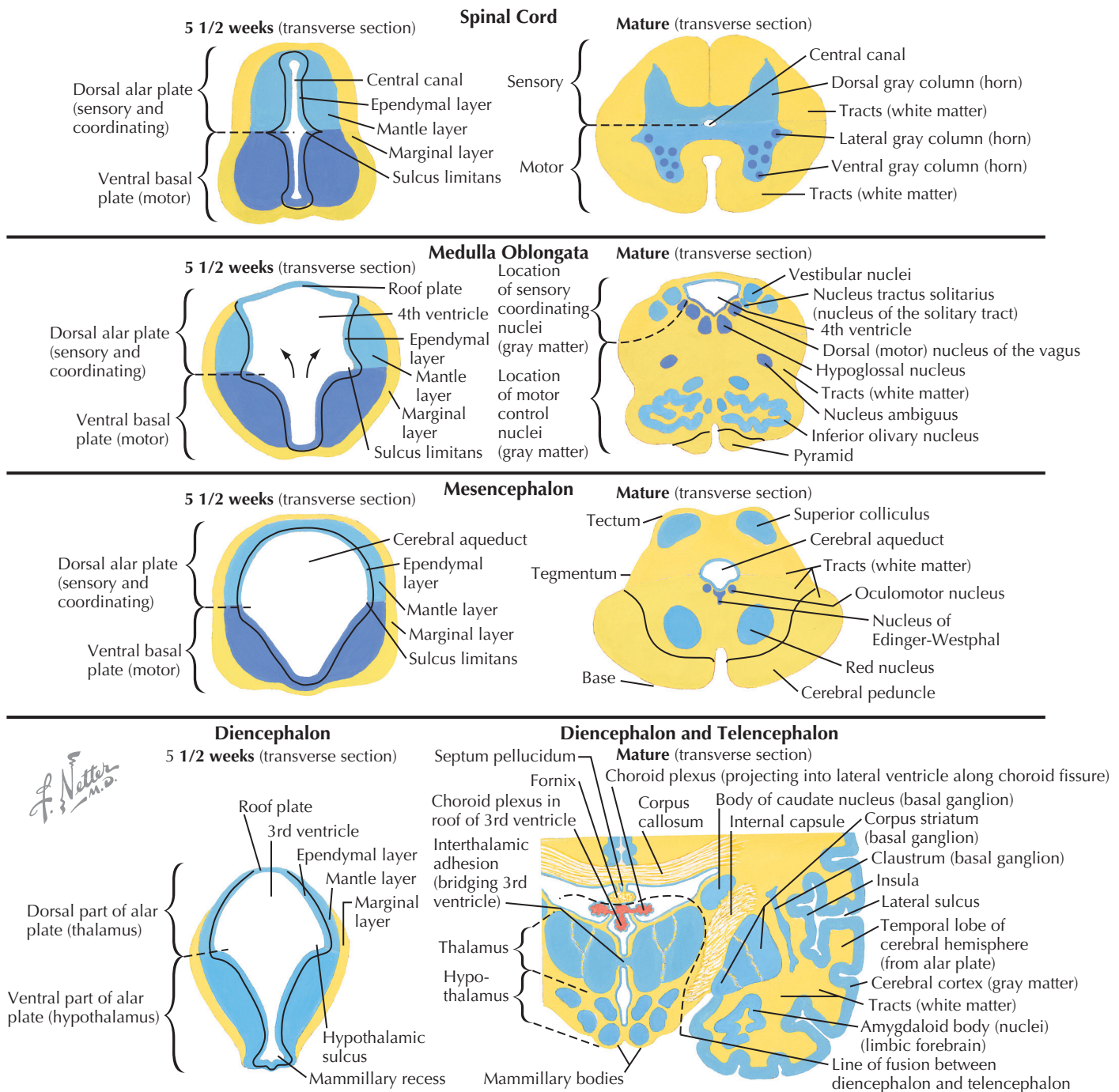




### 8.14 NEUROGENESIS AND CELL MIGRATION IN THE DEVELOPING NEOCORTEX

During the earliest phases of cortical development, neuroepithelial progenitor cells, with processes extending from the cell body to the inner ventricular surface and the outer pial surface, replicate. They form some neurons which populate the preplate region, and also generate the radial glial cells. The radial glial cells maintain their contact with the ventricular and pial surfaces, and give rise to post-mitotic cortical neurons. These neurons migrate towards the cortical surface along the radial glial processes, and populate the cortical plate. Cortical neurons accumulate in the cortical plate region in an inside-out fashion, with earliest generated neurons located deepest and latest generated neurons located more superficially. These

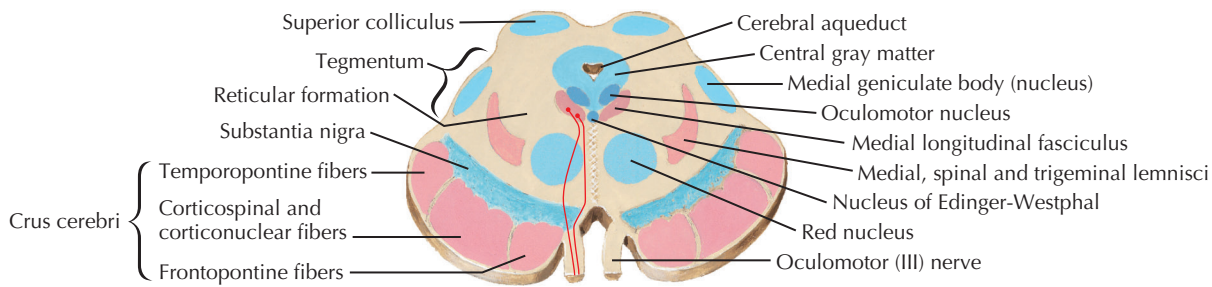
neurons differentiate to form association neurons (cortical-cortical connections) and projection neurons (to deeper subcortical structures). Most of the subplate neurons die, although some remain and differentiate into local (interstitial) interneurons. Cortical granule cells proliferate from the subependymal zone, and migrate both tangentially and radially into the cortical architecture. These neurons undergo abundant proliferation and migration postnatally in response to environmental stimuli. These complex processes of neurogenesis, proliferation, migration, differentiation, and integration into complex circuitry (intrinsic, projection, and association), followed by extensive postnatal dendritic and axonal maturation and connectivity, leaves cortical development vulnerable to a variety of insults and disruptions.



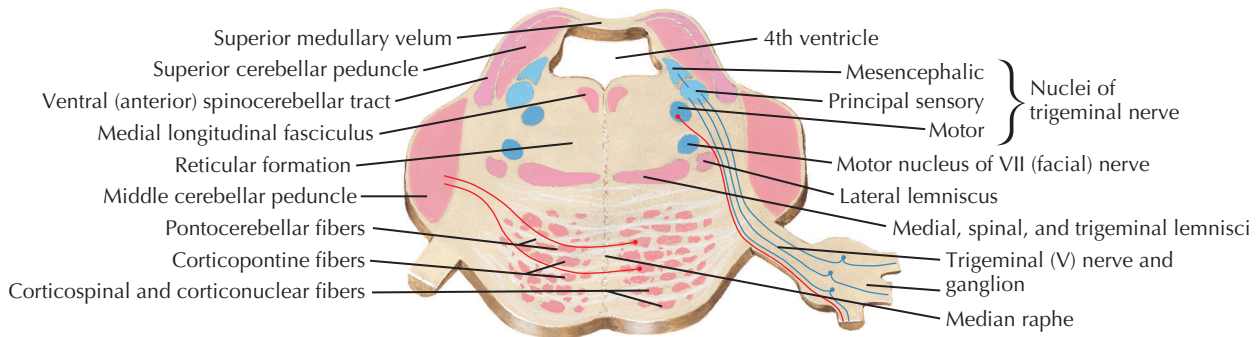
### 8.15 COMPARISON OF 5½-WEEK AND ADULT CENTRAL NERVOUS SYSTEM REGIONS

The relatively large ventricular system at 5½ weeks becomes comparatively smaller as the process of neuronal growth occurs. In adults, the central canal of the spinal cord becomes virtually obliterated and does not convey cerebrospinal fluid (CSF). The fourth ventricle opens up laterally; the sulcus limitans demarcates motor nuclei (medially) and sensory nuclei (laterally). The cerebral aqueduct remains very small. The

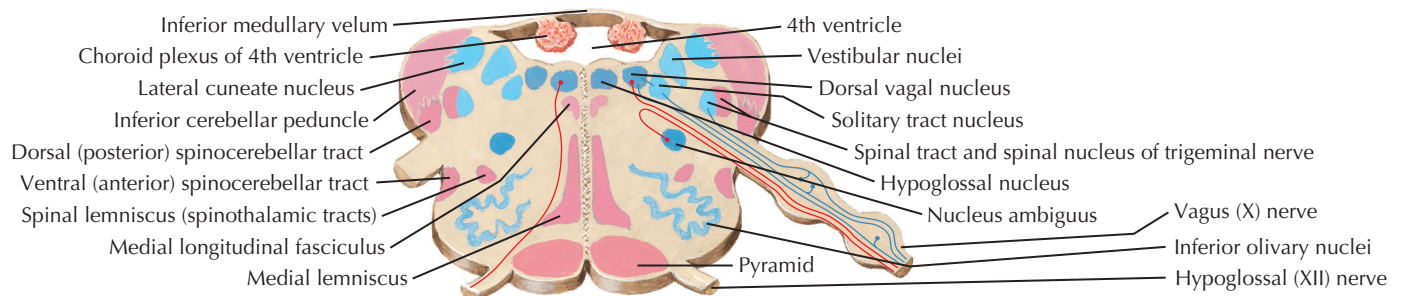
third ventricle narrows down to a slit. The lateral ventricles expand massively into a C-shape. The basal plate forms motor and autonomic structures whose axons leave the CNS. The alar plate forms sensory derivatives in the spinal cord and brain stem, and structures that migrate ventrally (the inferior olivary complex, the pontine nuclei, and the red nucleus). The rhombic lips, an alar derivative of the metencephalon, give rise to the entire cerebellum. The diencephalon and telencephalon are also alar plate derivatives.



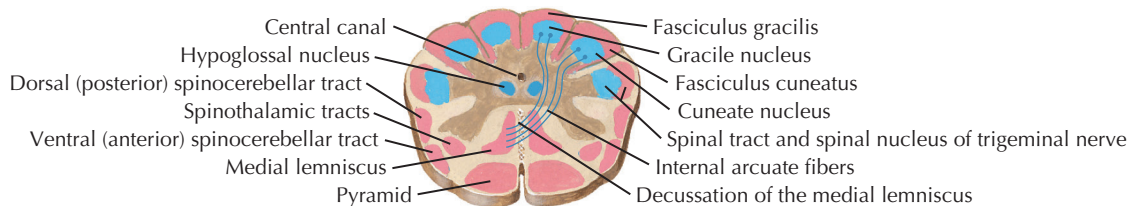
Section through midbrain at level of superior colliculi



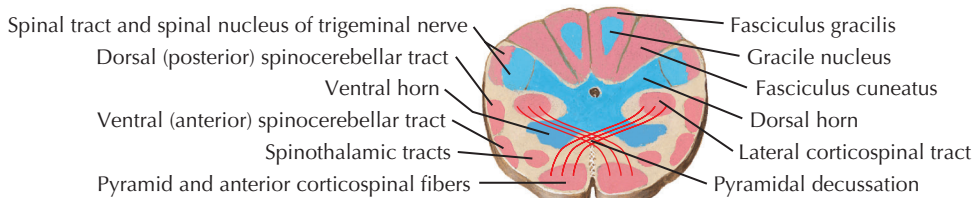
Section through pons at level of trigeminal nerves



Section through medulla oblongata at level of inferior olivary nuclei



Section through medulla oblongata at level of decussation of lemnisci



Section through medulla oblongata at level of pyramidal decussation

## 8.16 ALAR AND BASAL PLATE DERIVATIVES IN THE BRAIN STEM

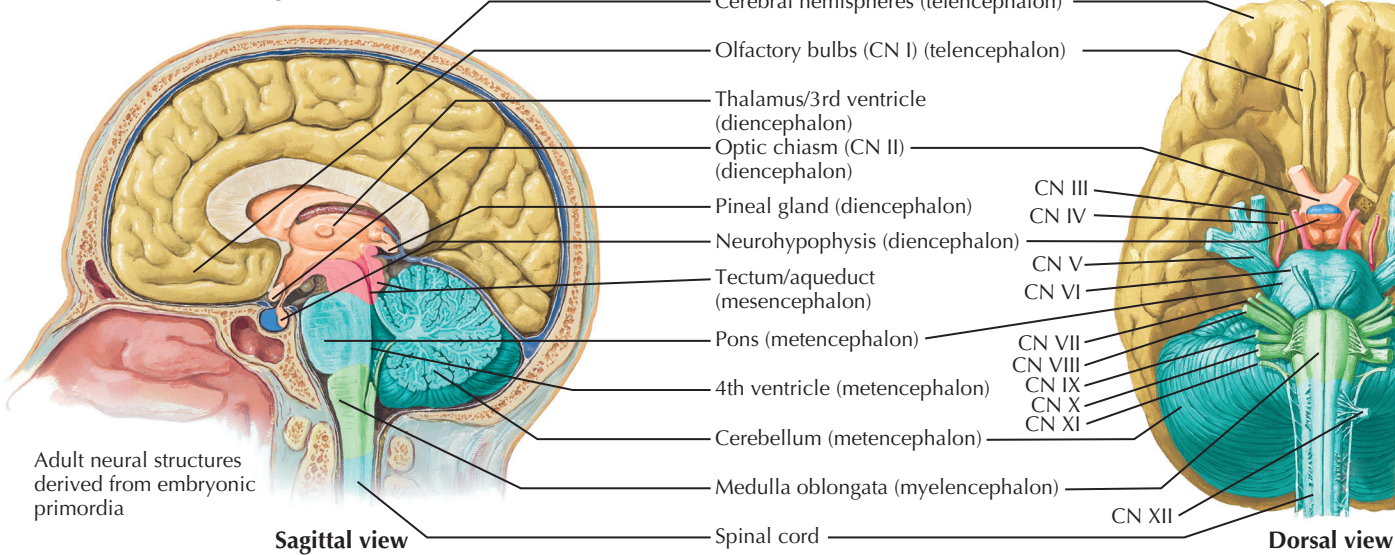
The general pattern of alar and basal plate derivatives seen in the spinal cord continues into the brain stem. The alar plate derivatives are the sensory nuclei (the rhombic lip from which

the cerebellum is derived) and nuclei that migrate ventrally to form such structures as the inferior olivary nuclei, the pontine nuclei, the red nucleus, and others. The basal plate derivatives are the motor and preganglionic autonomic nuclei.

*F. Netter M.D.*



Adult derivatives of brain primordia



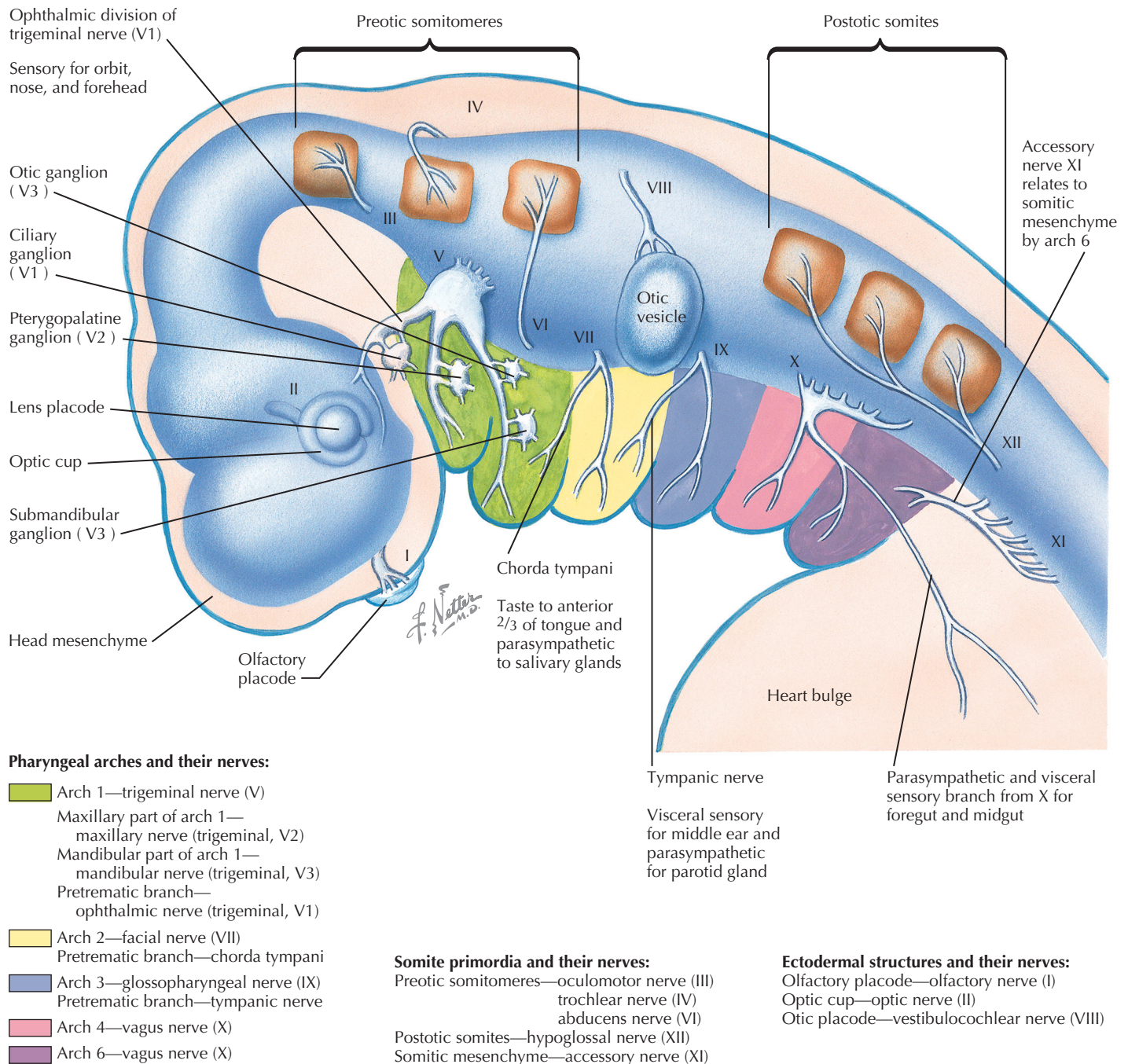
Adult derivatives of the forebrain, midbrain, and hindbrain

Forebrain	Telencephalon	Cerebral hemispheres (neocortex) Olfactory cortex (paleocortex) Hippocampus (archicortex) Basal ganglia/corpus striatum Lateral and 3rd ventricles	Nerves: Olfactory (I)
	Diencephalon	Optic cup/nerves Thalamus Hypothalamus Mammillary bodies Part of 3rd ventricle	Optic (II)
Midbrain	Mesencephalon	Tectum (superior, inferior colliculi) Cerebral aqueduct Red nucleus Substantia nigra Crus cerebelli	Oculomotor (III) Trochlear (IV)
Hindbrain	Metencephalon	Pons Cerebellum	Trigeminal (V) Abducens (VI) Facial (VII)
	Myelencephalon	Medulla oblongata	Acoustic (VIII) Glossopharyngeal (IX) Vagus (X) Hypoglossal (XI)

8.17 ADULT DERIVATIVES OF THE FOREBRAIN, MIDBRAIN, AND HINDBRAIN

The telencephalon has four major components: the cerebral cortex, the limbic forebrain structures, the basal ganglia, and the olfactory system. The diencephalon consists of two major structures: the thalamus and hypothalamus and two smaller structures, the epithalamus and subthalamus. The thalamus has extensive interconnections with the cerebral cortex and serves as a gateway to the telencephalon. The hypothalamus receives extensive input from the limbic forebrain and a variety of brain stem and visceral sensory sources, and regulates neuroendocrine and visceral autonomic functions. The midbrain consists of the colliculi, the tegmentum, and the

cerebral peduncles. The colliculi convey visual (superior) and auditory (inferior) information to higher regions of the brain and to brain stem and reflex pathways. The tegmentum houses important motor, sensory, and autonomic structures and plays a crucial role in consciousness and sleep. The cerebral peduncles are caudal continuations of the posterior limb of the internal capsule, and play a particularly important role in motor functions. The cerebellum plays an important role in coordinating movement, posture, locomotion, and equilibrium. The medulla and pons integrate the sensory, motor, and autonomic functions of the body via extensive connections through the cranial nerves, to which the spinal cord inputs contribute.



### 8.18 CRANIAL NERVE PRIMORDIA

The 12 pairs of cranial nerves exit the developing brain in sequence, except for cranial nerve XI, which exits most caudally. Cranial nerves I and II are CNS tracts, not peripheral nerves. The cranial nerves relate to surface placodes, head somites, or the pharyngeal arches, and they innervate all of the structures and tissues that derive from them. The vagus

nerve supplies arches 4 and 6. Although the otic, ciliary, pterygopalatine, and submandibular ganglia are associated anatomically with branches of the trigeminal nerve, these ganglia contain postganglionic neurons of the parasympathetic nervous system, receiving inputs from preganglionic neurons whose axons travel with CNs III, VII, and IX.

**Special sensory and somatomotor cranial nerve components**

Nerve	Primordium innervated	Neuron components
Olfactory (I) Optic (II) Vestibulocochlear (VIII)	Olfactory placode Optic cup Otic placode	Special sensory (olfaction) Special sensory (vision) Special sensory (hearing and balance)
Oculomotor (III)  Trochlear (IV) Abducens (VI) Hypoglossal (XII) Accessory (XI)	Preotic somitomere  Preotic somitomere Preotic somitomere Postotic somites Somitic mesenchyme by arch 6	Somatomotor to extraocular eye muscles Parasympathetics to ciliary ganglion (for pupil constrictor and ciliary muscle) Somatomotor to superior oblique muscle Somatomotor to lateral rectus muscle Somatomotor to tongue muscles Somatomotor to sternocleidomastoid and trapezius muscles

**Pharyngeal arch cranial nerve components**

Nerve	Arch	Neuron components
Trigeminal (V)	1	General sensory (face, orbit, nasal, and oral cavities) Branchiomotor (muscles of mastication, tensor tympani, tensor veli palatini)
Facial (VII)	2	Branchiomotor (muscles of facial expression, stylohyoid, posterior digastric, stapedius) Special sensory (taste to anterior two thirds of tongue) Parasympathetic to pterygopalatine and submandibular ganglia (for lacrimal glands, nasal mucosa, and salivary glands)
Glossopharyngeal (IX)	3	Visceral sensory to pharynx Branchiomotor to stylopharyngeus Parasympathetic to otic ganglion (for the parotid gland) Special sensory (taste to posterior tongue; carotid body and sinus)
Vagus (X)	4 and 6	Branchiomotor (pharynx and larynx) Visceral sensory (larynx, foregut below pharynx and midgut) General sensory to external acoustic meatus Parasympathetics (enteric ganglia of foregut and midgut) Special sensory (taste in laryngopharynx; carotid body and sinus)

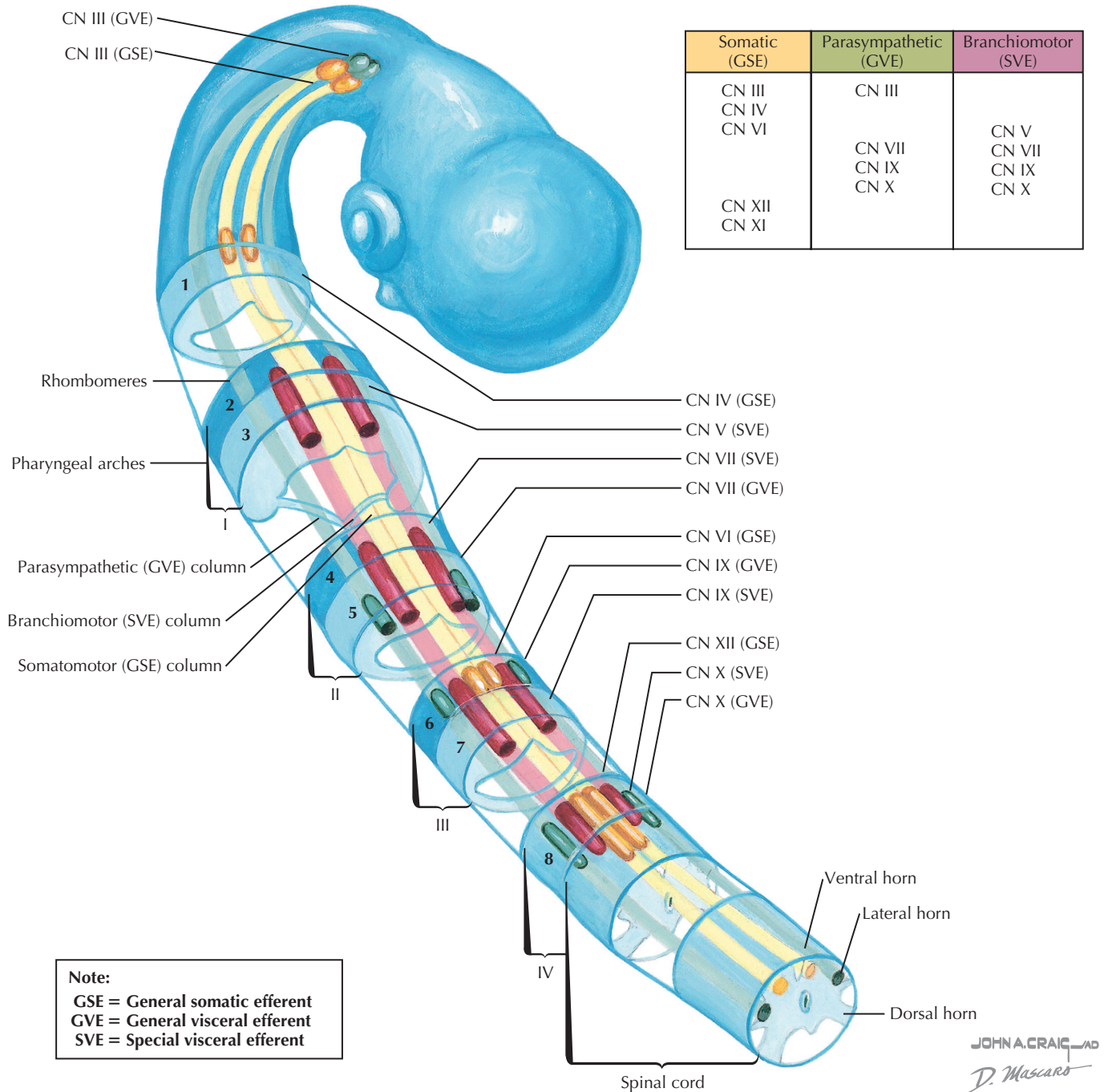
Reprinted with permission from Cochard L. *Netter's Atlas of Human Embryology, Updated Edition*. Philadelphia: Elsevier, 2012.

**8.19 CRANIAL NERVE NEURON COMPONENTS**

The pharyngeal arch nerves of the head and neck consist of several neuronal types. Most have branchiomotor neurons for skeletal muscles derived from arch mesenchyme, visceral sensory neurons for the inner endodermal linings of the arches (larynx and pharynx), and general sensory neurons for

surface ectoderm or lining of the stomodeum. The somites give rise to extraocular muscles and intrinsic muscles of the tongue. The placodes and optic cup relate to the special sensory organs of the head. Cranial nerves III, VII, IX, and X have preganglionic parasympathetic components that innervate ganglia distant from their nerves of origin.

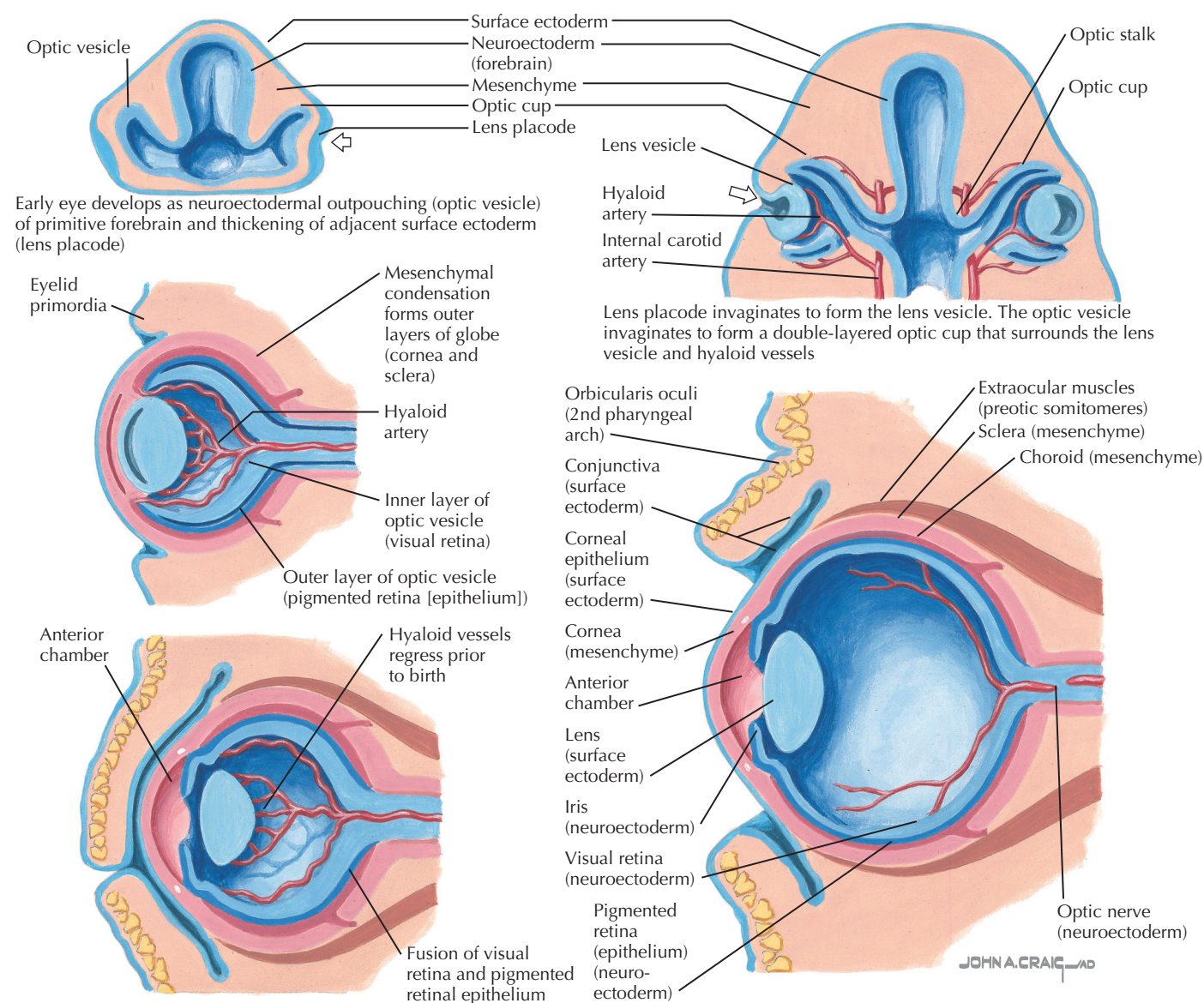




## 8.20 DEVELOPMENT OF MOTOR AND PREGANGLIONIC AUTONOMIC NUCLEI IN THE BRAIN STEM AND SPINAL CORD

Gray matter columns develop in the spinal cord for somatic lower motor neurons (ventral horn) and preganglionic autonomic neurons (lateral horn). These columns extend rostrally into the brain stem, maintaining the same general positional

relationship to each other but organized into a series of separate but aligned nuclei. A third group of nuclei develop in the rhombencephalon as branchiomotor neurons supplying pharyngeal arch muscles. Both the somatic motor and the branchiomotor neurons are classified as lower motor neurons and have axons exiting the CNS to synapse on skeletal muscle fibers.

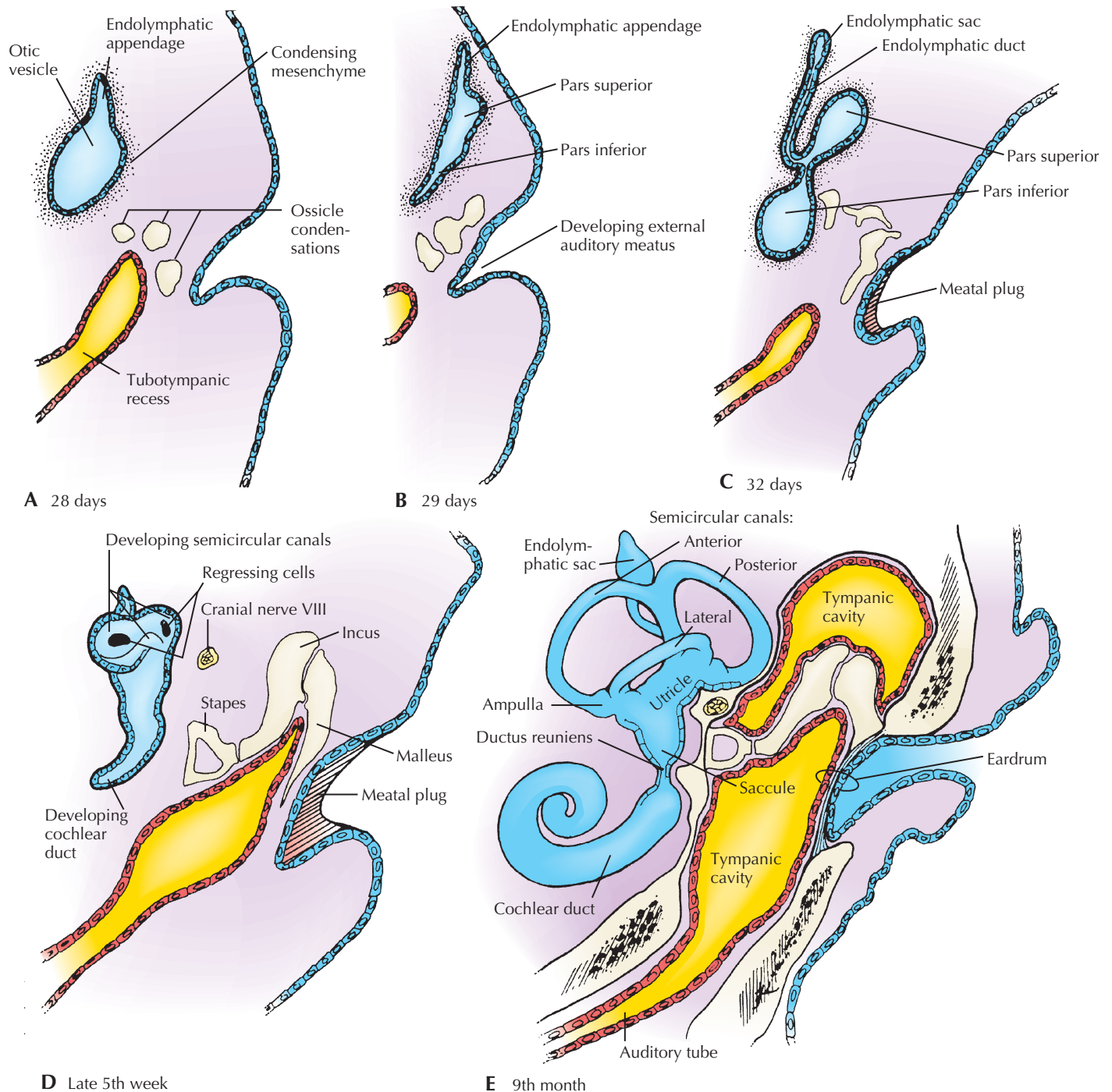


Primordium	Derivative	Related nerve
Optic cup	Retina, optic nerve, ciliary and iris epithelium, and pupil constrictor and dilator muscles	Optic nerve (II)
Head mesenchyme	Cornea, sclera, meninges, choroid, ciliary muscle and connective tissue, and iris connective tissue	Ophthalmic nerve (VI)
Somites	Extraocular eye muscles	III, IV, and VI
Surface ectoderm	Eyelid epidermis, conjunctiva, lacrimal gland	Ophthalmic nerve (VI)
2nd pharyngeal arch	Orbicularis oculi muscle	Facial nerve (VII)
Lens placode	Lens	

8.21 DEVELOPMENT OF THE EYE AND ORBIT

The retina and optic nerve develop as a double-layered extension of the neural tube, the optic cup. This extension surrounds the lens vesicle of surface origin and has a ventral groove to accommodate blood vessels. The iris and ciliary body are formed in part from optic cup epithelium. The two layers of the optic cup never fully fuse and can be separated

in the case of a retinal detachment. Connective tissues of mesodermal origin include the sclera, cornea, and vascular choroid layer. The extraocular muscles derive from somitomeres. The epidermis of the eyelids develops from surface ectoderm and is continuous with the conjunctiva and corneal epithelium.



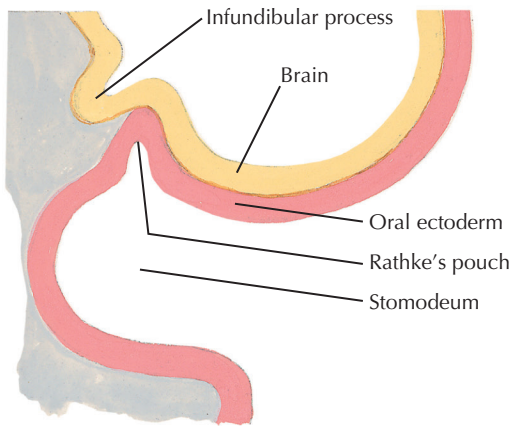
Reprinted with permission from Schoenwolf G, Bleyl S, Brauer P, et al. *Larsen's Human Embryology*, 4th ed. Philadelphia: Elsevier, 2008.

## 8.22 DEVELOPMENT OF THE EAR

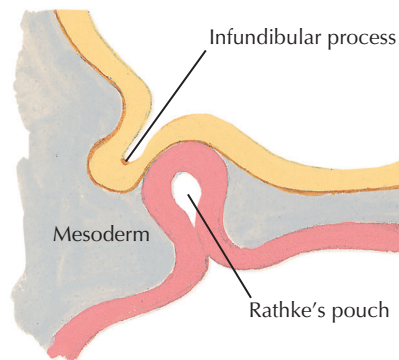
The ear consists of the outer component (the auricle, external auditory meatus to the eardrum); the middle component (the ossicles [malleus, incus, stapes]); and the inner component

(the bony and membranous labyrinths, the cochlea, and the semicircular canals). The outer ear derives from the first pharyngeal groove, the middle ear from the first pharyngeal pouch, and the inner ear from the otic placode.





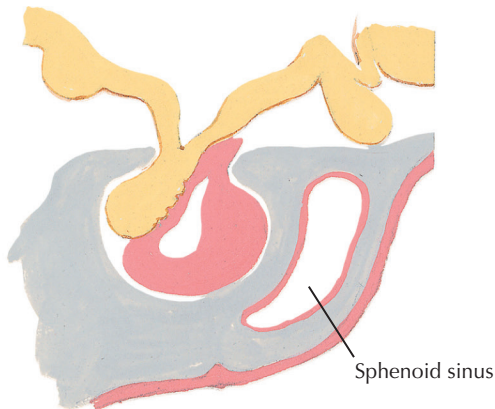
1. Beginning formation of Rathke's pouch and infundibular process



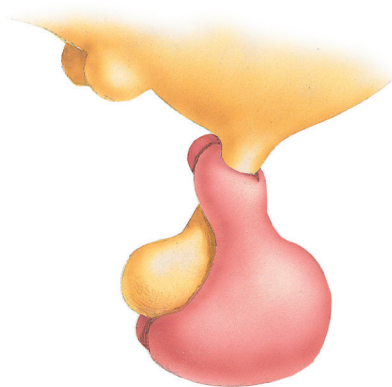
2. Neck of Rathke's pouch constricted by growth of mesoderm



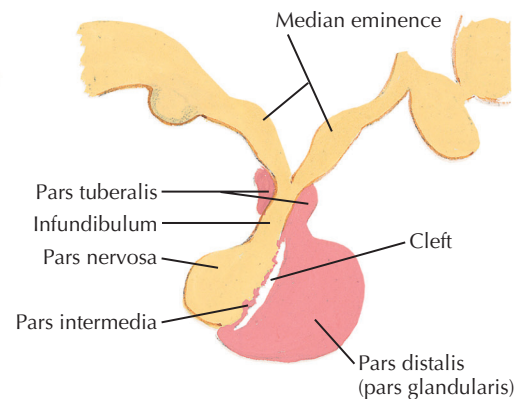
3. Rathke's pouch "pinched off"



4. Pinched-off segment conforms to neural process, forming pars distalis, pars intermedia, and pars tuberalis



5. Pars tuberalis encircles infundibular stalk (lateral surface view)



6. Mature form

*F. Netter M.D.*

### Pituitary hormones

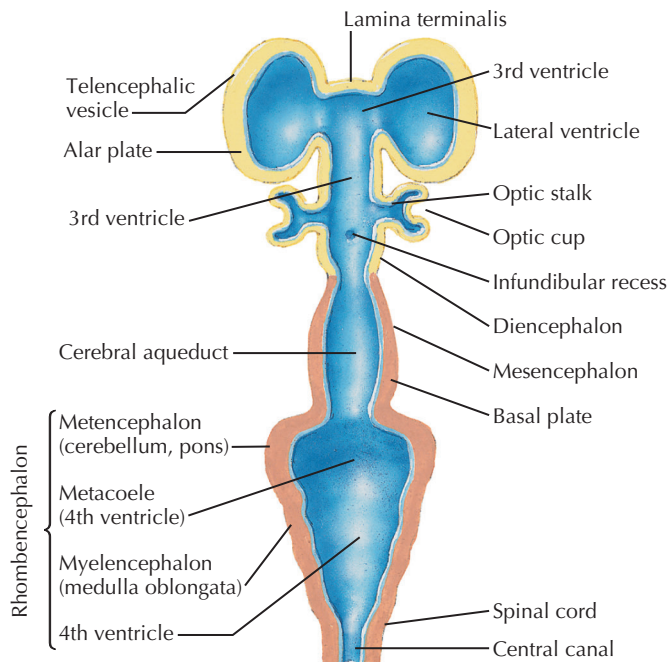
From the anterior lobe (pars distalis)		From the posterior lobe (pars nervosa)
Follicle-stimulating hormone (FSH)	Thyroid-stimulating hormone (TSH)	Vasopressin
Luteinizing hormone (LH)	Adrenocorticotrophic hormone (ACTH)	Oxytocin
Prolactin	Growth hormone (GH)	

## 8.23 DEVELOPMENT OF THE PITUITARY GLAND

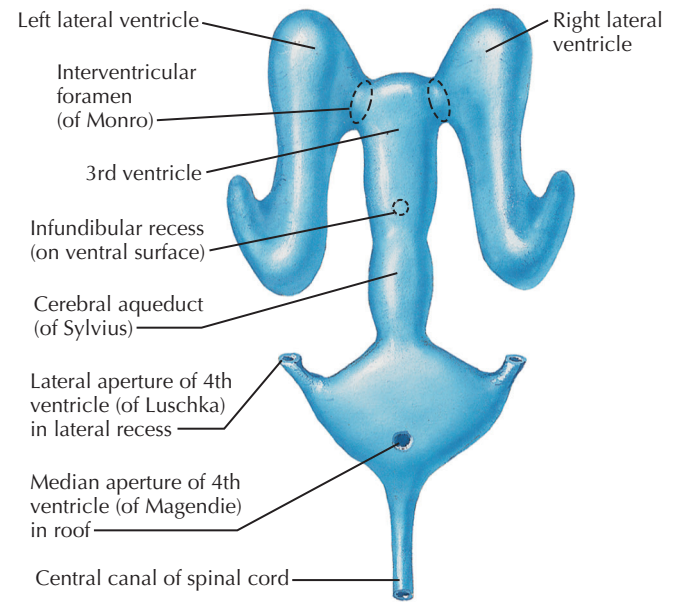
The pituitary gland develops from outgrowth of two separate primordia. The anterior lobe (adenohypophysis) derives from the roof of the stomodeum and encircles the base of the posterior lobe (neurohypophysis). The posterior lobe derives from the brain and possesses axonal processes from the hypothalamus that secrete oxytocin and vasopressin into the

general circulation. The anterior lobe contains pituicytes that respond to releasing and inhibitory factors from neurons of the brain that are delivered through a private vascular channel, the hypophyseal-portal system, and secreted into this circulation hormones such as follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone, adrenocorticotrophic hormone, and growth hormone.

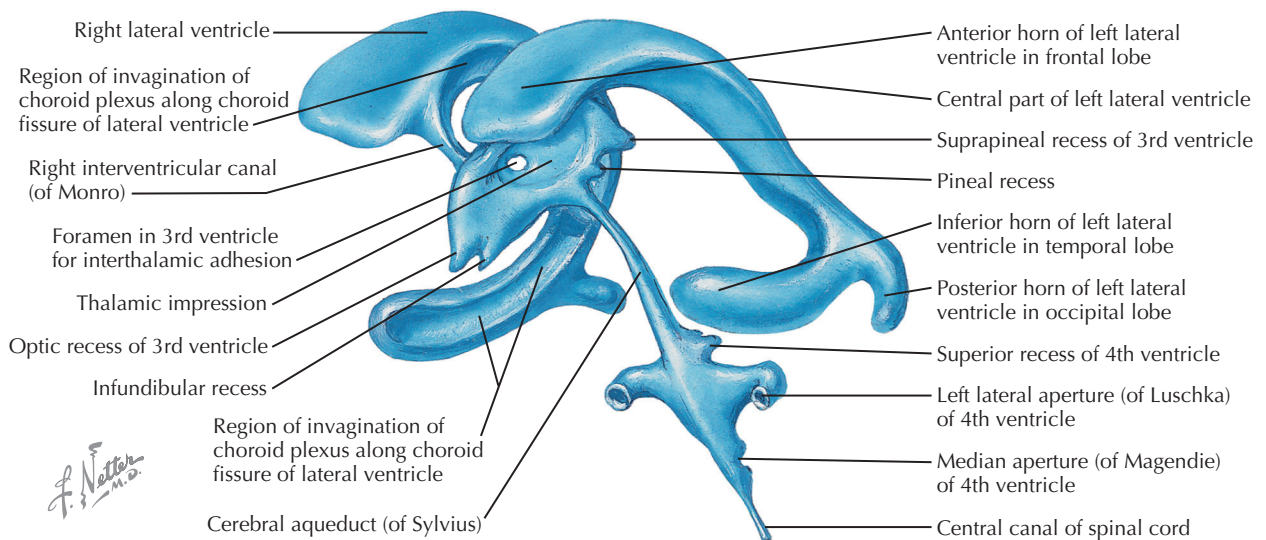
Frontal section (ventral to sulcus limitans) at 36 days



Ependymal lining of cavities of brain at 3 months



Ependymal lining of cavities of brain at 9 months (birth)



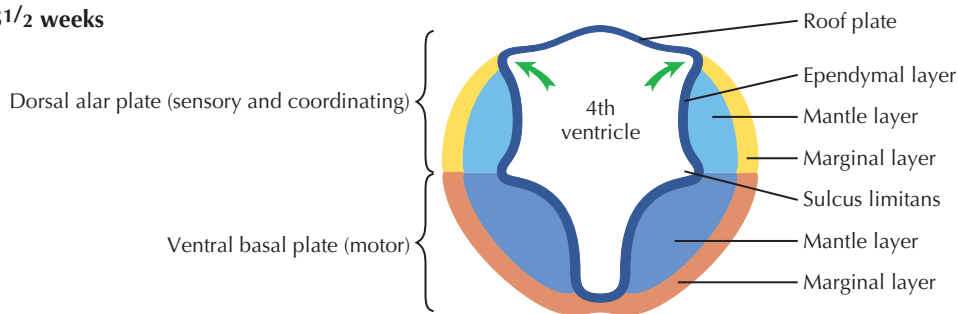
## 8.24 DEVELOPMENT OF THE VENTRICLES

The rapid growth of the brain stem and the forebrain alters the uniform appearance of the ventricles. The C-shaped lateral ventricles follow the growth of the telencephalon, with limited access into the third ventricle through the interventricular foramen of Monro. The narrow cerebral aqueduct remains very small in the upper mesencephalon and opens into the rhomboid-shaped and expanding fourth ventricle. The foramina of Magendie (medial) and Luschka (lateral) in the fourth ventricle allow flow from the ventricular system into the developing cisterns of the subarachnoid space. CSF reenters the venous system through the arachnoid granulations, one-way valves that allow drainage from the subarachnoid space into the dural (venous) sinuses, especially the superior sagittal sinus.

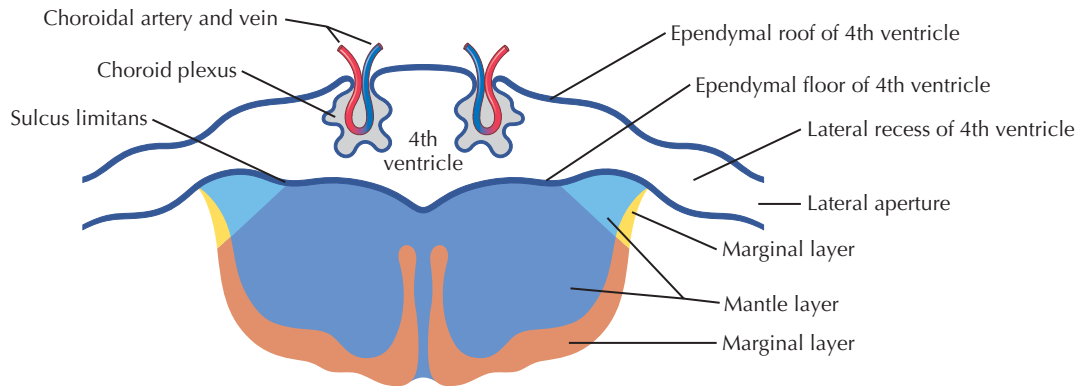
### CLINICAL POINT

The C-shaped form of the ventricular system follows from the development of the primary brain vesicles, with the flexures and disproportionate neural development. The lateral ventricles are associated with the telencephalon, the third ventricle with the diencephalon, the cerebral aqueduct with the mesencephalon, and the fourth ventricle with the rhombencephalon (metencephalon [pons] and myelencephalon [medulla]). The foramina of Magendie and Luschka, which allow for the escape of CSF into the subarachnoid space, are already patent at the end of the first trimester. An obstruction of internal CSF flow results in internal hydrocephalus. A common site for such an obstruction is atresia of the cerebral aqueduct, with enlarged third and lateral ventricles. Another site of possible obstruction occurs with Dandy-Walker syndrome, a malformation of the fourth ventricle that includes atresia of the foramina of Magendie and Luschka, internal hydrocephalus of the entire ventricular system, hypoplasia of the cerebellum, and posterior fossa cyst formation.

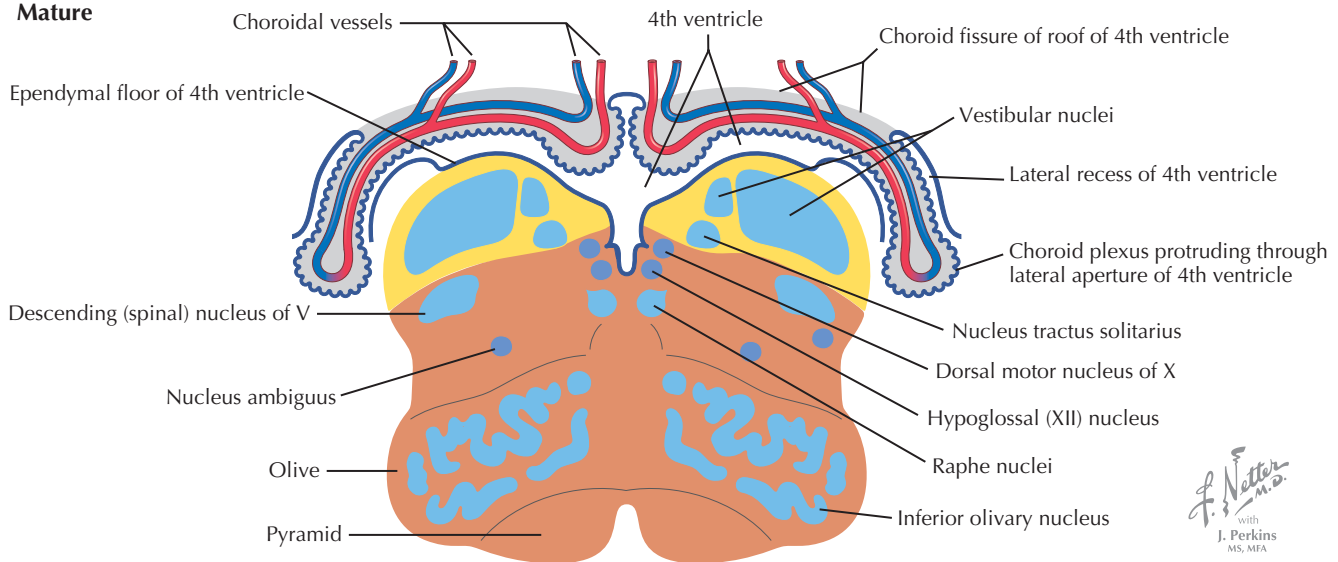
5½ weeks



3½ months



Mature



*F. Netter M.D.*  
with  
J. Perkins  
MS, MFA

## 8.25 DEVELOPMENT OF THE FOURTH VENTRICLE

The expansion of the fourth ventricle from the original central canal of the rhombencephalon into its mature form is a complex process. The sulcus limitans is conspicuous early in development (5½ weeks), and the original lateral walls expand outward and lie down horizontally (5½ months) as the roof plate expands to both sides. As a result, the sulcus limitans becomes a landmark at the dorsal boundary of the medulla

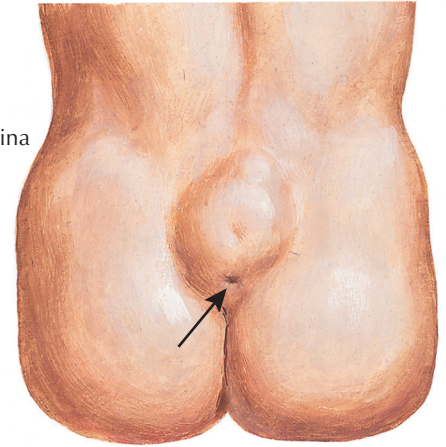
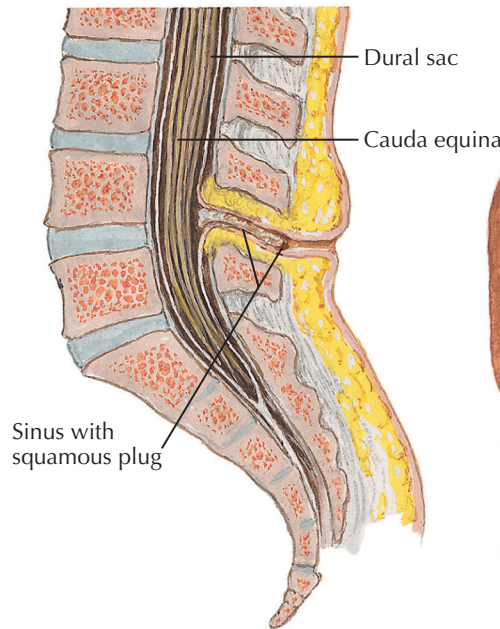
on the floor of the fourth ventricle, separating the motor structures medially from the sensory structures laterally. The lateral aperture of the fourth ventricle (the foramen of Luschka) opens into the subarachnoid space. In their mature form (bottom illustration), these paired lateral apertures are major channels between the internal and external circulation of the CSF and must remain open so as to prevent internal hydrocephalus.



Spinal bifida occulta

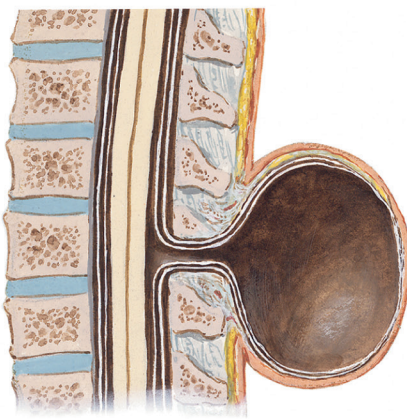


Dermal sinus

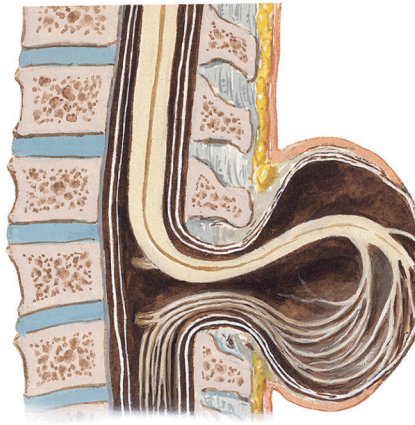


Fat pad overlying spina bifida occulta. Tuft of hair or only skin dimple may be present, or there may be no external manifestation. Dermal sinus also present in this case (arrow)

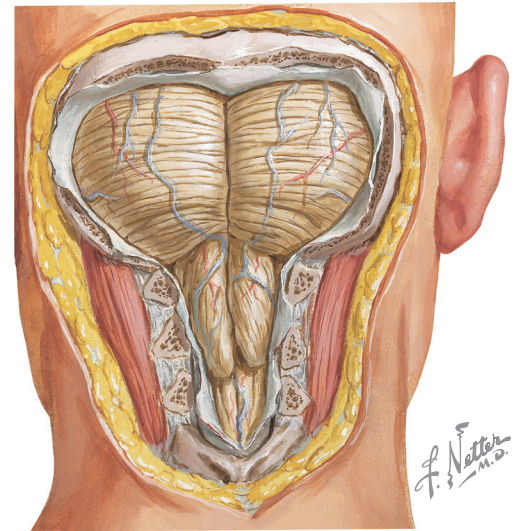
Types of spina bifida aperta with protrusion of spinal contents



Meningocele



Meningomyelocele



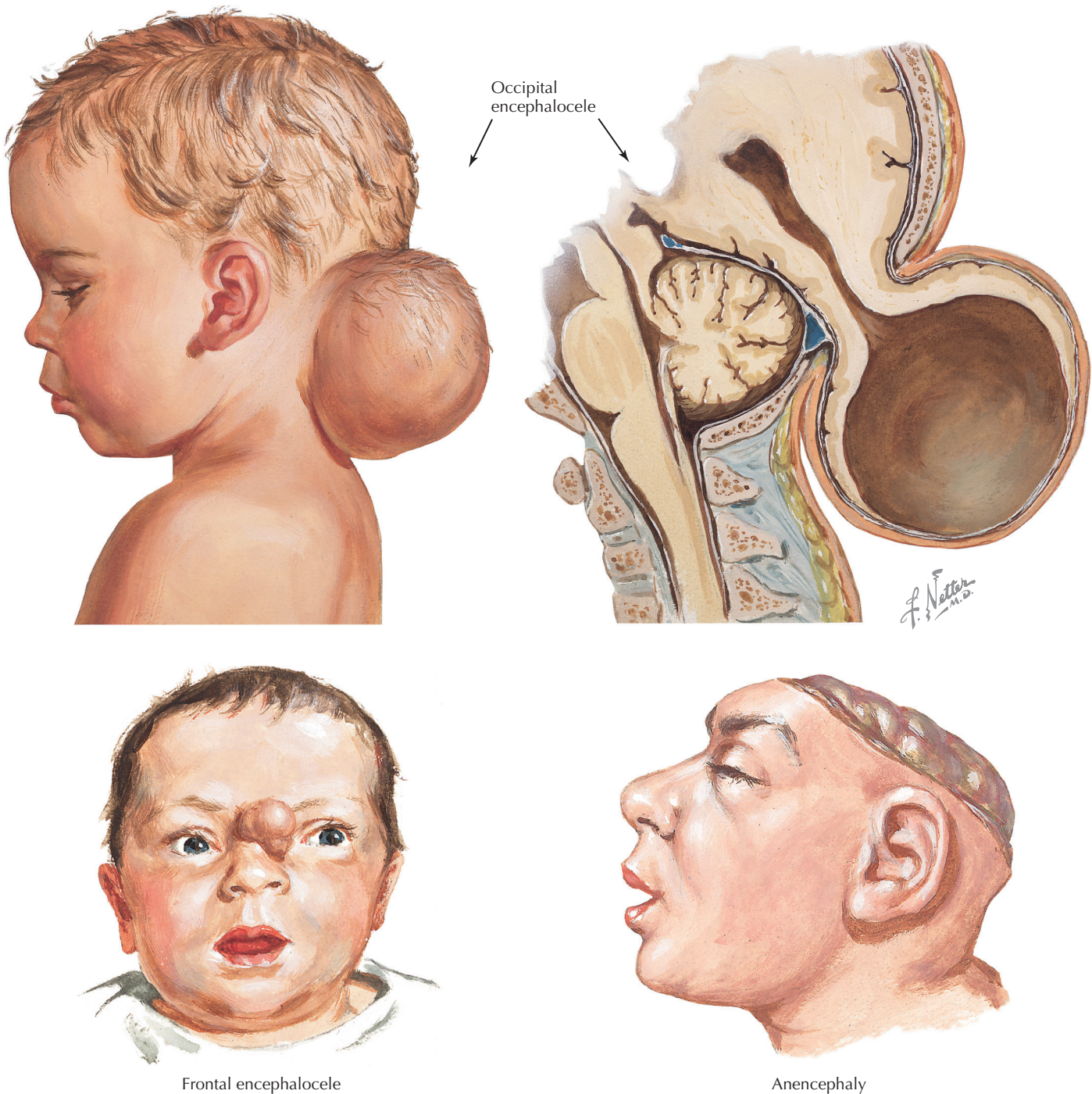
Arnold-Chiari syndrome decompression

## 8.26 NEURAL TUBE DEFECTS

Spina bifida occurs when a vertebral arch fails to develop; the neural tube cannot move below the surface, and somite sclerotome cells cannot migrate over it to complete the vertebral arch. The spinal cord may be exposed on the surface (myeloschisis), which involves severe functional deficits or death and a high likelihood of infection. A protrusion may form, usually in the lumbar region, into which spinal cord and nerve roots

may protrude (meningomyelocele) or in which CSF is present (meningocele). When these defects are repaired, the brain stem may herniate (Arnold-Chiari malformation), and extensive functional deficits may be present, such as loss of bladder and bowel function and loss of motor function and sensation in the lower extremities. In its most benign form, spina bifida occulta may be manifested by a small sinus or a tuft of hair at the site of defect.





### 8.27 DEFECTS OF THE BRAIN AND SKULL

Defects of the rostral portion of the neural tube involve the brain and skull. If the occipital bone or other midline bones fail to ossify, meninges and possibly brain tissue may protrude into a sac (encephalocele). If the rostral (cranial) neuropore fails to close, the brain and much of the skull fail to develop (anencephaly) and the tissue that is present is exposed to the

external environment. This condition is incompatible with life. The Arnold-Chiari malformation may occur with or without spina bifida such as in a meningocele; in this malformation, the tonsils of the cerebellum herniate through the foramen magnum and can disrupt vital brain stem functions, resulting in death.



## Section II **REGIONAL NEUROSCIENCE**

An anatomical illustration of the human nervous system. The brain is shown at the top, with the spinal cord extending down the back. The peripheral nervous system is depicted as a network of nerves branching out from the spinal cord to various parts of the body, including the arms and legs. The illustration uses a color-coded system: blue for the brain and spinal cord, and red for the peripheral nerves. The background is a light green gradient.

### **9. Peripheral Nervous System**

Introduction and Basic Organization

Somatic Nervous System

Autonomic Nervous System

### **10. Spinal Cord**

### **11. Brain Stem and Cerebellum**

Brain Stem Cross-Sectional Anatomy

Cranial Nerves and Cranial Nerve Nuclei

Reticular Formation

Cerebellum

### **12. Diencephalon**

### **13. Telencephalon**



# 9

## PERIPHERAL NERVOUS SYSTEM

### Introduction and Basic Organization

- 9.1 Schematic of the Spinal Cord with Sensory, Motor, and Autonomic Components of Peripheral Nerves
- 9.2 Anatomy of a Peripheral Nerve
- 9.3 Nerve Compression and Pressure Gradients
- 9.4 Peripheral Nerve Injury and Degeneration in a Compression Neuropathy
- 9.5 Relationship of Spinal Nerve Roots to Vertebrae
- 9.6 Lumbar Disc Herniation: L4–L5 and L5–S1
- 9.7 Sensory Channels: Reflex and Cerebellar
- 9.8 Sensory Channels: Lemniscal
- 9.9 Motor Channels: Basic Organization of Lower and Upper Motor Neurons
- 9.10 Autonomic Channels
- 9.11 Cutaneous Receptors
- 9.12 Pacinian Corpuscles
- 9.13 Interoceptors
- 9.14 Skin and Its Nerves
- 9.15 The Neuromuscular Junction and Neurotransmission
- 9.16 Physiology of the Neuromuscular Junction
- 9.17 Major Structures and Proteins in the Normal Neuromuscular Junction
- 9.18 Neuroeffector Junctions

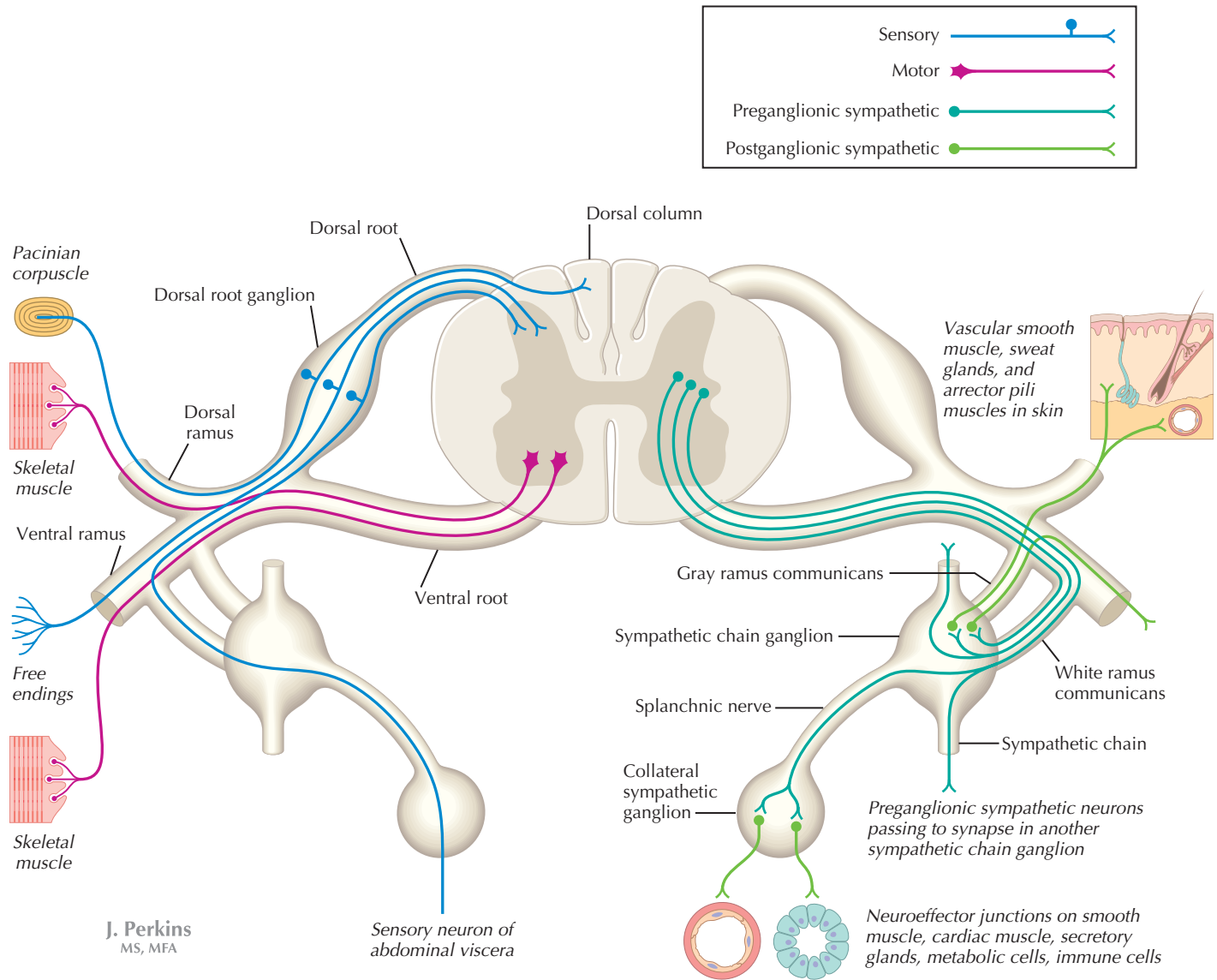
### Somatic Nervous System

- 9.19 Dermatomal Distribution
- 9.20 Cutaneous Distribution of Peripheral Nerves
- 9.21 Cutaneous Nerves of the Head and Neck
- 9.22 Cervical Plexus in Situ
- 9.23 Cervical Plexus
- 9.24 Phrenic Nerve
- 9.25 Thoracic Nerves
- 9.26 Brachial Plexus
- 9.27 Dermatomes of the Upper Limb
- 9.28 Cervical Disc Herniation
- 9.29 Cutaneous Innervation of the Upper Limb
- 9.30 The Scapular, Axillary, and Radial Nerves above the Elbow
- 9.31 Radial Nerve in the Forearm
- 9.32 Musculocutaneous Nerve
- 9.33 Median Nerve
- 9.34 Carpal Tunnel Syndrome
- 9.35 Ulnar Nerve
- 9.36 Lumbar Plexus
- 9.37 Sacral and Coccygeal Plexuses
- 9.38 Femoral and Lateral Femoral Cutaneous Nerves
- 9.39 Obturator Nerve

- 9.40 Sciatic and Posterior Femoral Cutaneous Nerves
- 9.41 Tibial Nerve
- 9.42 Common Peroneal Nerve

### Autonomic Nervous System

- 9.43 General Schema
- 9.44 Autonomic Innervation of the Immune System and Metabolic Organs
- 9.45 Reflex Pathways
- 9.46 Cholinergic and Adrenergic Synapses
- 9.47 Schematic of Cholinergic and Adrenergic Distribution to Motor and Autonomic Structures
- 9.48 Autonomic Distribution to the Head and Neck: Medial View
- 9.49 Autonomic Distribution to the Head and Neck: Lateral View
- 9.50 Schematic of Autonomic Distribution to the Head and Neck
- 9.51 Autonomic Distribution to the Eye
- 9.52 Autonomic Innervation of the Nasal Cavity
- 9.53 Schematic of the Pterygopalatine and Submandibular Ganglia
- 9.54 Schematic of the Otic Ganglion
- 9.55 Innervation of the Limbs
- 9.56 Thoracic Sympathetic Chain and Splanchnic Nerves
- 9.57 Innervation of the Tracheobronchial Tree
- 9.58 Innervation of the Heart
- 9.59 Abdominal Nerves and Ganglia
- 9.60 Nerves of the Esophagus
- 9.61 Innervation of the Stomach and Proximal Duodenum
- 9.62 Nerves of the Stomach and Duodenum
- 9.63 Innervation of the Small and Large Intestines
- 9.64 Nerves of the Small Intestine
- 9.65 Nerves of the Large Intestine
- 9.66 Enteric Nervous System: Longitudinal View
- 9.67 Enteric Nervous System: Cross-sectional View
- 9.68 Autonomic Innervation of the Liver and Biliary Tract
- 9.69 Autonomic Innervation of the Pancreas
- 9.70 Schematic of Innervation of the Adrenal Gland
- 9.71 Innervation of the Adrenal Gland
- 9.72 Autonomic Pelvic Nerves and Ganglia
- 9.73 Nerves of the Kidneys, Ureters, and Urinary Bladder
- 9.74 Innervation of the Kidneys and Upper Ureter
- 9.75 Innervation of the Urinary Bladder and Lower Ureter
- 9.76 Innervation of the Male Reproductive Organs
- 9.77 Innervation of the Female Reproductive Organs



## INTRODUCTION AND BASIC ORGANIZATION

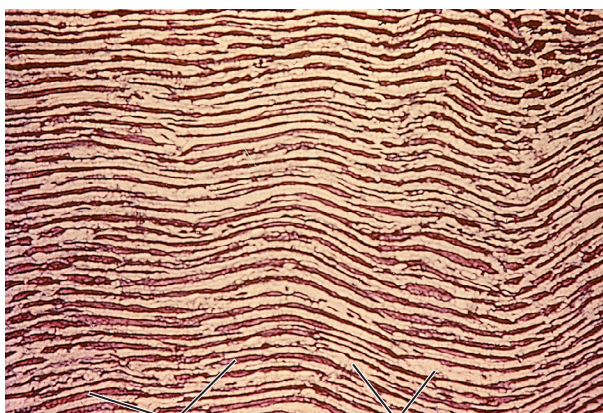
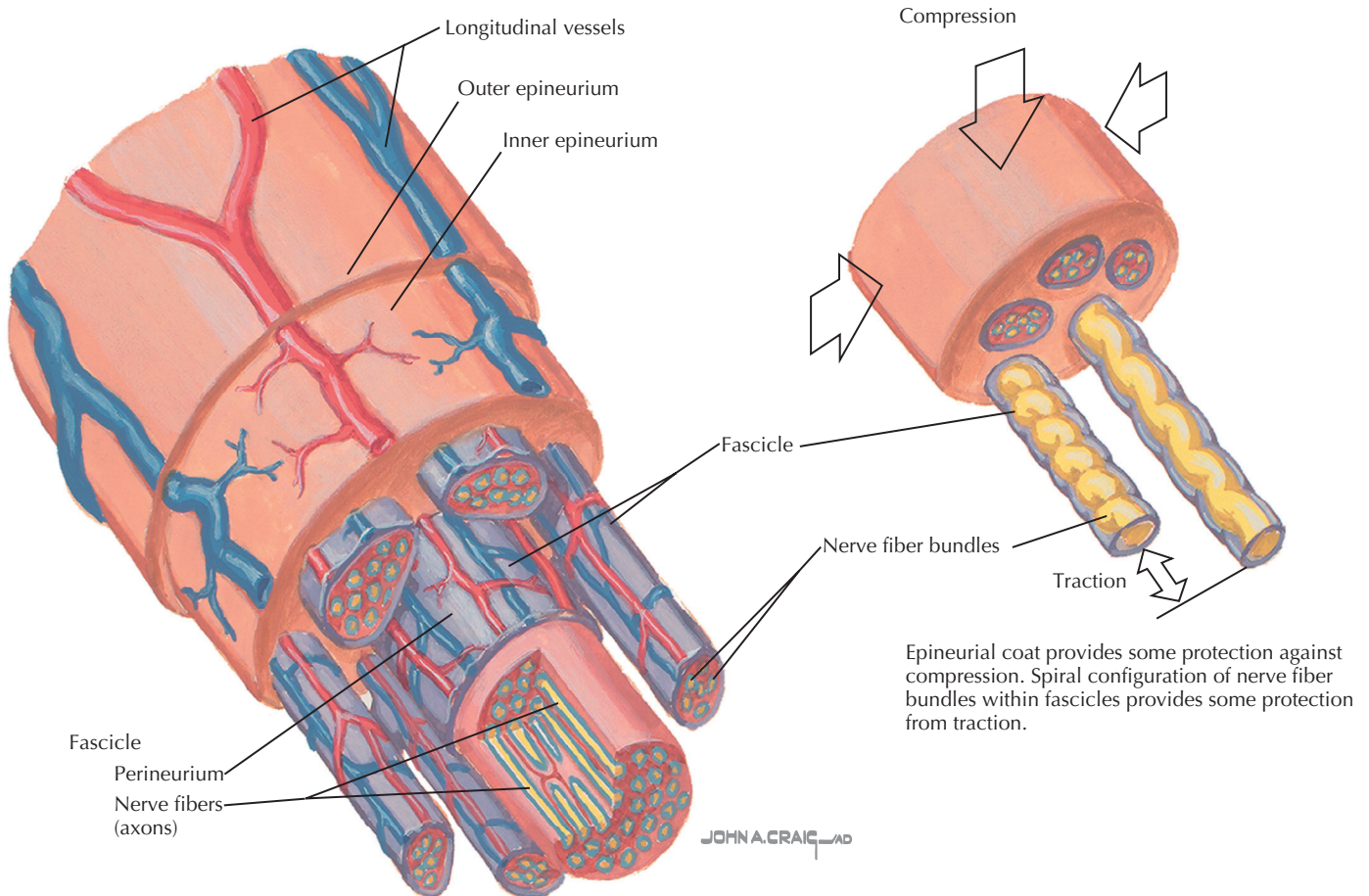
### 9.1 SCHEMATIC OF THE SPINAL CORD WITH SENSORY, MOTOR, AND AUTONOMIC COMPONENTS OF PERIPHERAL NERVES

Peripheral nerves consist of axons from primary sensory neurons, lower motor neurons (LMNs), and preganglionic and postganglionic autonomic neurons. The primary sensory axons have sensory receptors (transducing elements) at their peripheral (distal) ends, contiguous with the initial segment of the axon. The proximal portion of the axon enters the central nervous system (CNS) and terminates in secondary sensory nuclei associated with reflex, cerebellar, and lemniscal channels. LMNs in the anterior horn of the spinal cord send axons via the ventral (anterior) roots to travel in peripheral nerves to skeletal muscles, with which they form neuromuscular junctions. The autonomic preganglionic neurons send axons via the ventral roots to terminate in autonomic ganglia

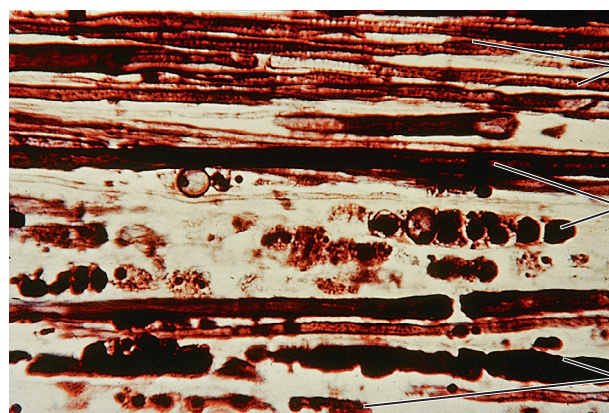
or in the adrenal medulla. Postganglionic neurons send axons into splanchnic or peripheral nerves and form neuroeffector junctions with smooth muscle, cardiac muscle, secretory glands, metabolic cells, and cells of the immune system.

#### CLINICAL POINT

Peripheral nerves form through the union of dorsal and ventral roots and by subsequent branching, similar to the process that occurs through the brachial plexus. The resultant terminal peripheral nerves contain limited categories of axonal types, including LMN axons (both alpha and gamma); primary sensory axons (both myelinated and unmyelinated); and autonomic axons (mainly postganglionic sympathetic axons). Destructive lesions in peripheral nerves may cause flaccid paralysis of innervated skeletal muscles (with loss of tone and denervation atrophy); loss of some or all aspects of somatic sensation in the innervated territory; and some autonomic dysfunction resulting from loss of sympathetic innervation (e.g., vasodilation and lack of sweating). An irritative lesion of a peripheral nerve is usually manifested as pain radiating to the innervated territory.



Peripheral nerve in longitudinal section, demonstrating the longitudinal array of axons (densely stained), with segments surrounded by myelin (clear areas). Fiber stain.



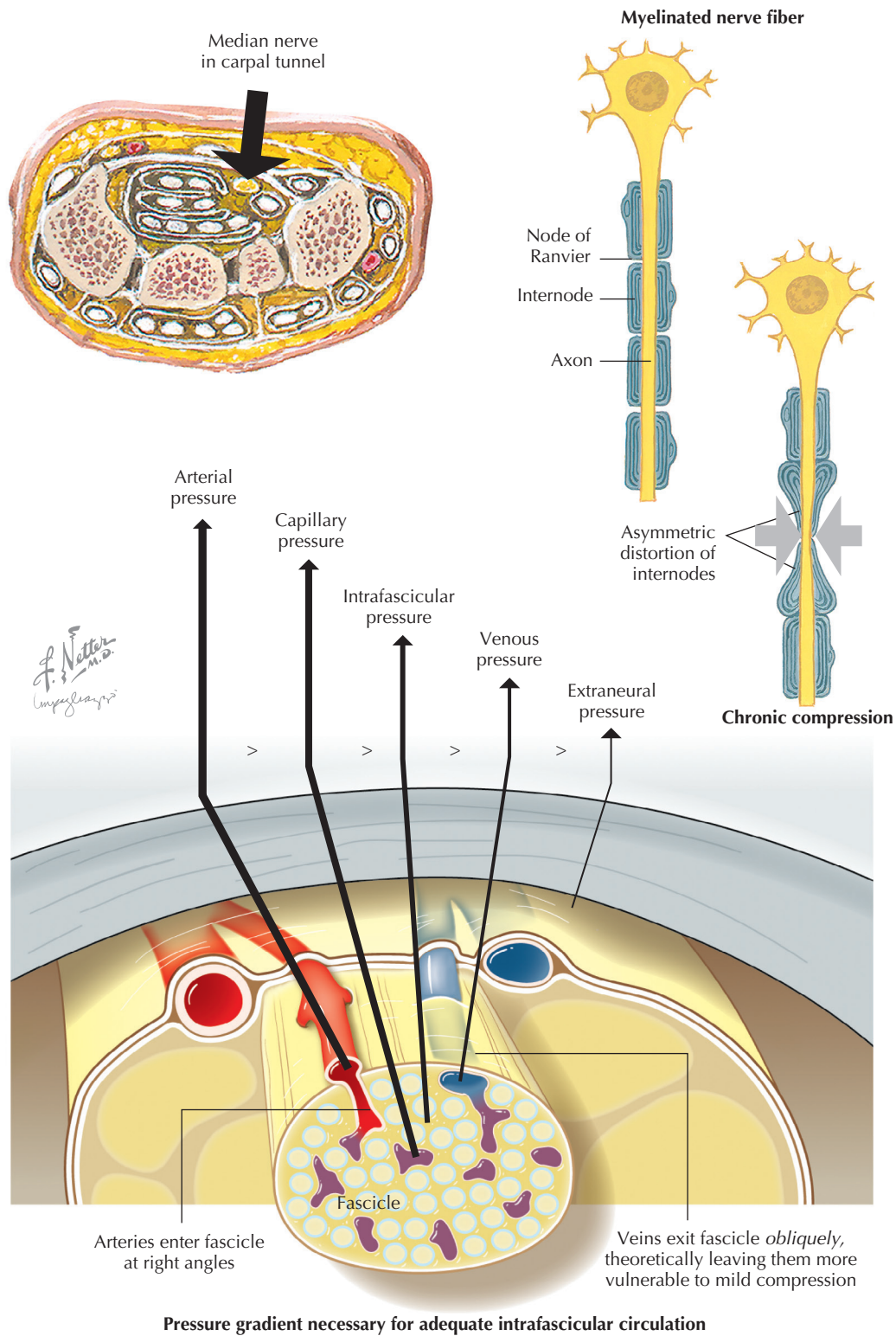
Peripheral nerve undergoing Wallerian degeneration following an insult. Some axons at the top are relatively intact. Other axons on the bottom are starting to degenerate, and a group of axons in the middle are forming globules of axons and myelin remnants, and are undergoing dissolution (see Plate 9.4 for full description of this process). Osmic acid myelin stain.

## 9.2 ANATOMY OF A PERIPHERAL NERVE

A peripheral nerve is made up of unmyelinated and myelinated axons; the connective sheaths with which they are associated; and local blood vessels, the vasa nervorum. Unmyelinated axons are surrounded by the cytoplasm of Schwann cells, called Schwann cell sheaths. Each individual segment of a myelinated axon is wrapped by a myelin sheath, provided by an individual Schwann cell. The bare space between each myelin sheath is called a node of Ranvier and is the site on the membrane where sodium channels are present and is also the

site of initiation or reinitiation of the action potential. Endoneurium is loose, supportive, connective tissue that is found between individual axons within a fascicle. Fascicles of multiple axons are wrapped by a sheath of supportive cells and collagenous connective tissue; this perineurium functions as a blood-nerve barrier and helps to protect the axons from local diffusion of potentially damaging substances. This perineurial barrier can be disrupted in neuropathic conditions such as diabetic neuropathy. The epineurium is the outermost layer of supportive connective tissue that wraps the entire nerve.

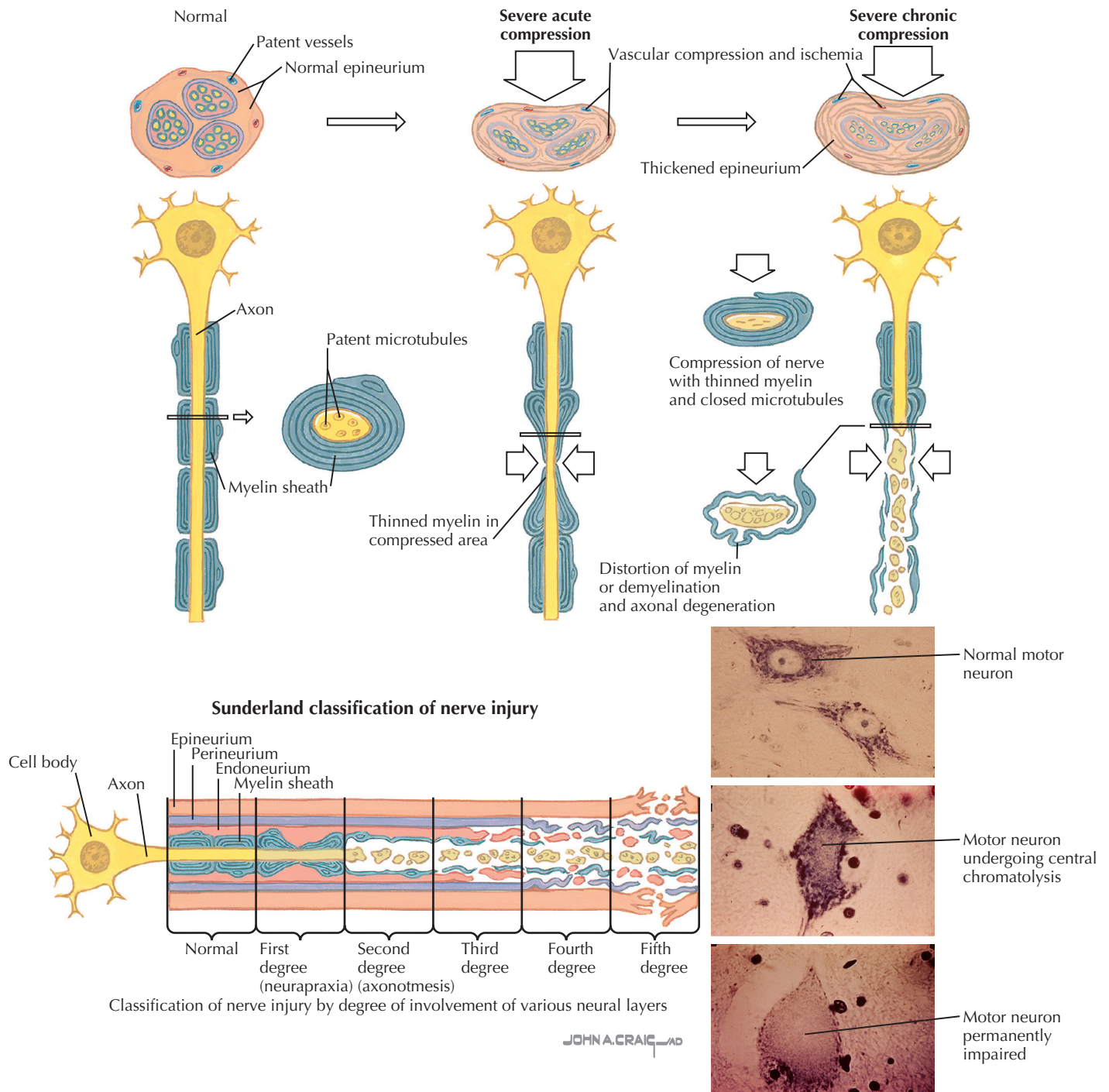




### 9.3 NERVE COMPRESSION AND PRESSURE GRADIENTS

With chronic compression of a nerve, such as median nerve entrapment in carpal tunnel syndrome, internodes of large myelinated axons are distorted (accompanied by repeated demyelination and remyelination), and both ischemia and endoneurial edema occur. Endoneurial edema can induce venous congestion and increase fluid pressure, resulting in

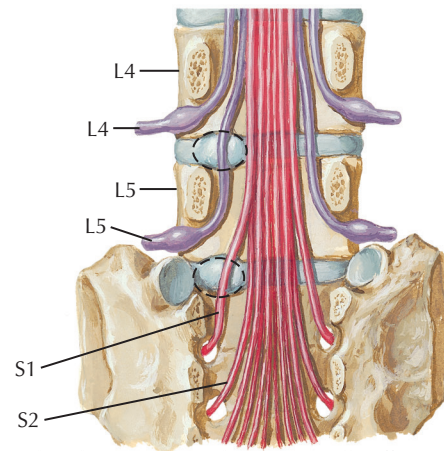
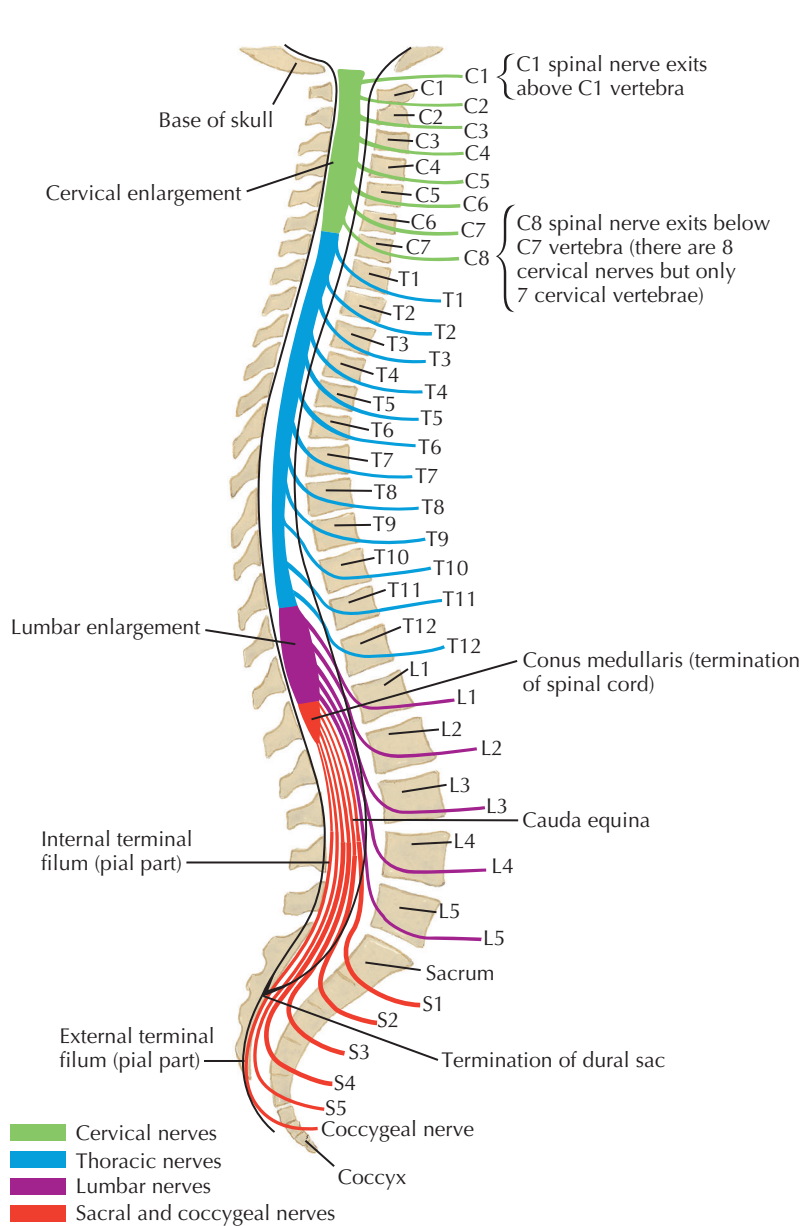
metabolic, physiologic, and anatomic damage and dysfunction of the affected peripheral nerves. Affected axons exhibit impaired axoplasmic transport, both anterograde and retrograde. Diabetes increases the susceptibility of peripheral nerves to entrapment, with endoneurial edema and impaired axoplasmic transport. Chronic compression can lead to degeneration of the affected axons.



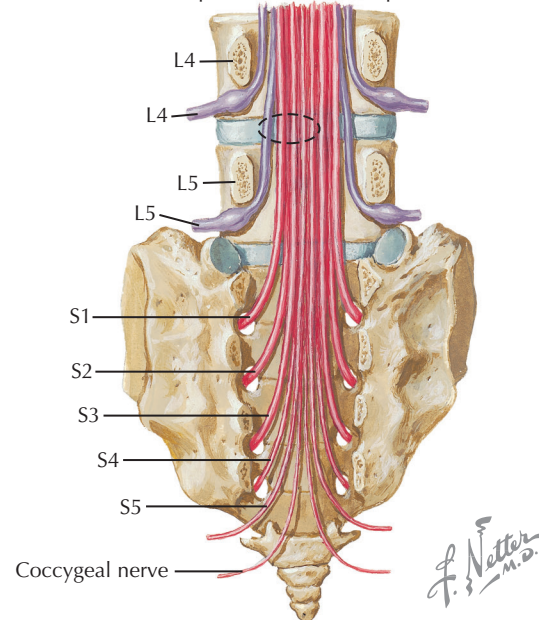
#### 9.4 PERIPHERAL NERVE INJURY AND DEGENERATION IN A COMPRESSION NEUROPATHY

If a peripheral nerve is compressed or damaged, a series of reactions takes place within the neurons whose axons have been damaged and in the supportive tissue. At the site of the injury, axonal damage and thinning of the myelin or frank demyelination can occur. Distal to the site of the injury, the peripheral portion of the axon can degenerate (called Wallerian degeneration), resulting in the breaking up and dissolution of the peripheral axon. The Schwann cells responsible for myelinating the degenerating axons also break up and degenerate. However, the basement membrane remains intact, providing a scaffold through which future regenerating axons can

be directed. The central (proximal) portion of the neuron can undergo changes called central chromatolysis. The Nissl bodies (endoplasmic reticulum) break up into individual ribosomes, the cell body swells, and the neuron shifts its metabolism to structural and reparative synthetic products that attempt to save the neuron and permit it to try to recover from the injury. If successful, this process gradually reverses, and the neuron begins to sprout a peripheral axonal extension, seeking to reattach to the target from which it was disrupted. The Schwann cells proliferate and generate new myelin sheaths around the regrowing axon, but the intersegmental distances of the new myelin sheath are shorter than the original distances and the myelin sheath is thinner; thus, the regenerated axon shows a slower conduction velocity than the original intact axon.



Lumbar disc protrusion does not usually affect nerve exiting above disc. Lateral protrusion at disc level L4-5 affects L5 spinal nerve, not L4 spinal nerve. Protrusion at disc level L5-S1 affects S1 spinal nerve, not L5 spinal nerve



Medial protrusion at disc level L4-5 rarely affects L4 spinal nerve but may affect L5 spinal nerve and sometimes S1-4 spinal nerves.

## 9.5 RELATIONSHIP OF SPINAL NERVE ROOTS TO VERTEBRAE

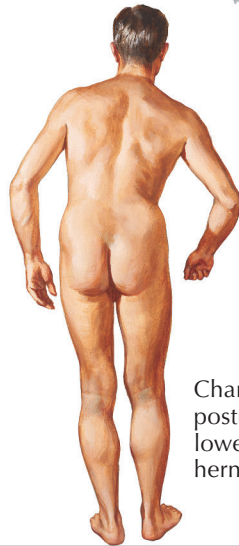
The dorsal (posterior) and ventral (anterior) roots of the spinal cord segments extend from the spinal cord as peripheral axons, invested initially with meninges. As the axons enter the peripheral nervous system, they become associated with Schwann cells for myelination and support. The roots exit through the intervertebral foramina, compact openings between the vertebrae where herniated discs (nucleus pulposus) may impinge on the nerve roots and produce sensory or motor symptoms. Sensory and motor axons travel with the dorsal and ventral rami of peripheral nerves. Autonomic axons (myelinated) course from the ventral roots into the white (preganglionic) rami communicans and synapse in autonomic ganglia. The ganglion cells give rise to postganglionic axons (unmyelinated) that course through the gray rami communicans and join the peripheral nerves.

### CLINICAL POINT

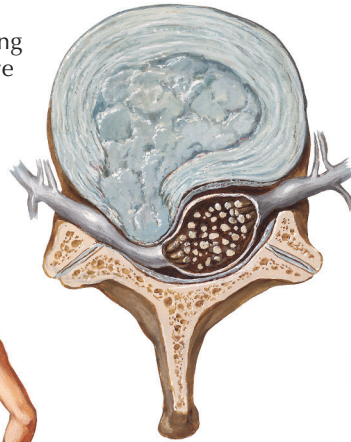
The longitudinal growth of the spinal column outstrips the longitudinal growth of the spinal cord; as a consequence, the spinal cord in adults ends adjacent to the L1 vertebral body. Nerve roots heading for intervertebral foramina below L1 extend caudally through the subarachnoid space in the lumbar cistern, forming the cauda equina. Damage to the cauda equina can occur as the result of tumors, such as ependymomas and lipomas, or of a prolapsed intervertebral disc. It is common for symptoms to occur gradually and be irregular because of the ample room in the lumbar cistern for nerve roots to move. Radicular pain often is experienced in a sciatic distribution, with progressive loss of sensation in radicular patterns. A more caudal location of the obstructing mass may lead to loss of sensation in regions of sacral innervation in the perineal (saddle) zone. Loss of bowel, bladder, and erectile function also may occur. More rostral lesions may result in flaccid paralysis of the legs.



Cross section showing compression of nerve root



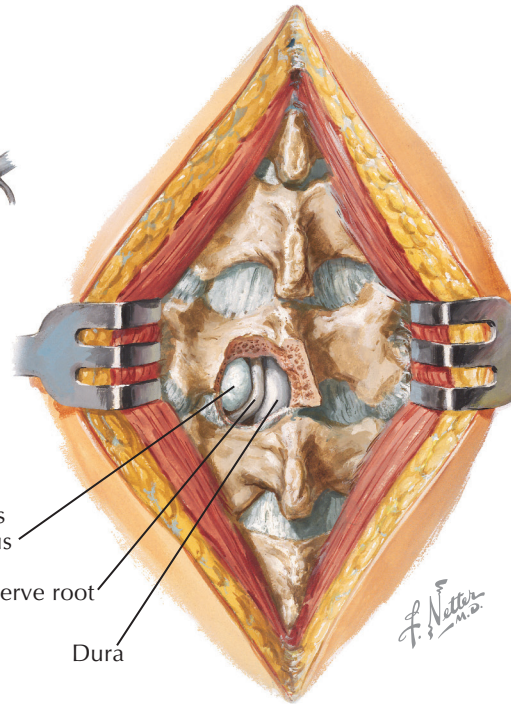
Characteristic posture in left-sided lower lumbar disk herniation



Nucleus pulposus

Nerve root

Dura



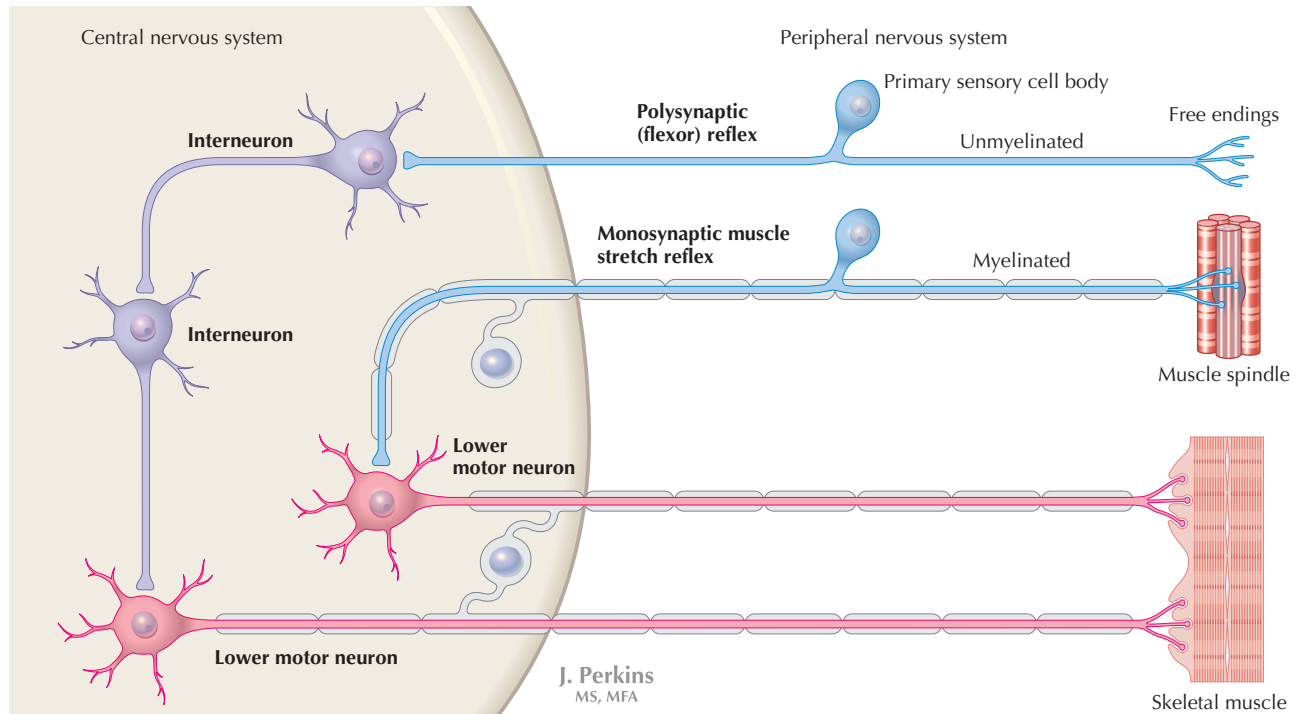
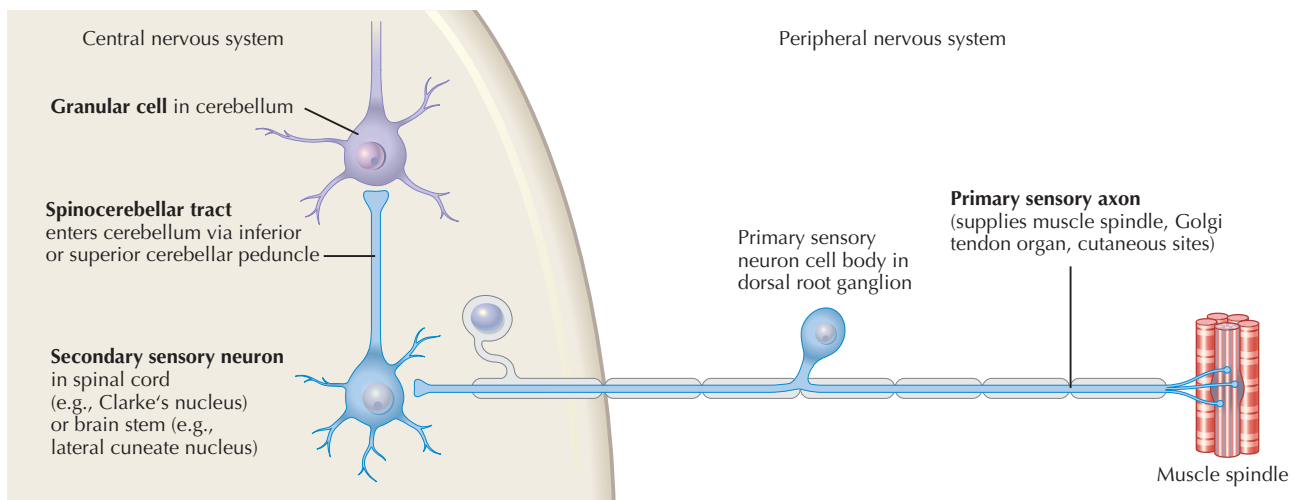
Surgical exposure of lower lumbar disk herniation

Clinical features of herniated lumbar nucleus pulposus

Level of herniation	Pain	Numbness	Weakness	Atrophy	Reflexes
<p><b>L4-5 disk; 5th lumbar nerve root</b></p>	<p>Over sacroiliac joint, hip, lateral thigh and leg</p>	<p>Lateral leg, first 3 toes</p>	<p>Dorsiflexion of great toe and foot; difficulty walking on heels; foot drop may occur</p>	Minor	Changes uncommon in knee and ankle jerks, but internal hamstring reflex diminished or absent
<p><b>L5-S1 disk; 1st sacral nerve root</b></p>	<p>Over sacroiliac joint, hip, postero-lateral thigh and leg to heel</p>	<p>Back of calf, lateral heel, foot to toe</p>	<p>Plantar flexion of foot and great toe may be affected; difficulty walking on toes</p>	<p>Gastrocnemius and soleus</p>	<p>Ankle jerk diminished or absent</p>

## 9.6 LUMBAR DISC HERNIATION: L4-L5 AND L5-S1

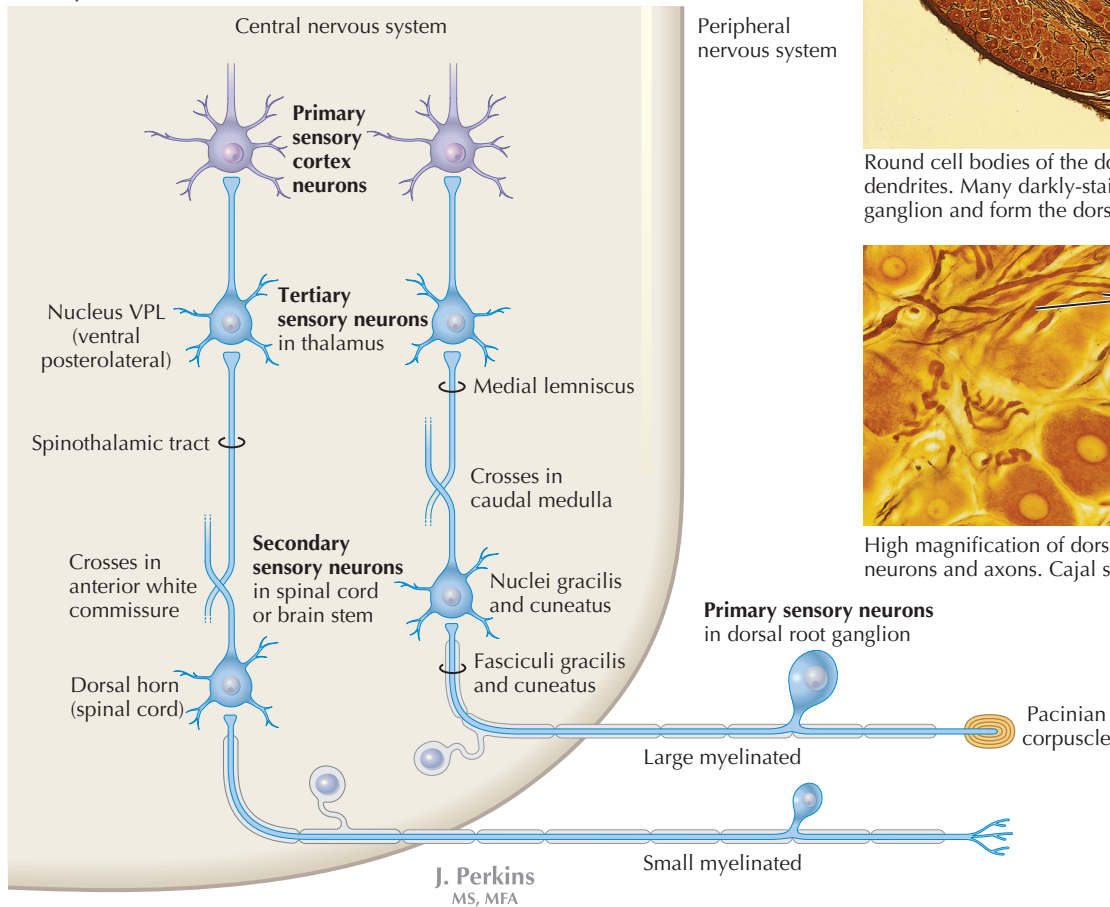
Characteristics and clinical manifestation of lower lumbar disc herniations at L4-L5 and L5-S1.

**A. Sensory Channels—Reflex****B. Sensory Channels—Cerebellar****9.7 SENSORY CHANNELS: REFLEX AND CEREBELLAR**

Primary sensory axons communicate with secondary sensory neurons in reflex, cerebellar, and lemniscal channels, carrying transduced information from the periphery into the CNS. **A**, The reflex channels interconnect primary sensory axons with anterior horn cells (LMNs) through one or more synapses to achieve unconscious reflex motor responses to sensory input. These responses can be elicited in an isolated spinal cord devoid of connections from the brain. The monosynaptic reflex channels connect primary sensory axons from muscle spindles, via the dorsal roots, directly with LMNs involved in muscle stretch reflex contraction; this is the only monosynaptic reflex seen in the human CNS. Polysynaptic reflex channels are directed particularly toward flexor (withdrawal) responses through one or more interneurons to produce coordinated

patterns of muscle activity to remove a portion of the body from a potentially damaging or offending stimulus. This polysynaptic channel can spread ipsilaterally and contralaterally through many segments. **B**, Primary somatosensory axons carrying unconsciously processed information from muscles, joints, tendons, ligaments, and cutaneous sources enter the CNS via dorsal roots and synapse with secondary sensory neurons in the spinal cord or caudal brain stem. These secondary sensory neurons convey information, initially derived from the periphery, to the ipsilateral cerebellum via spinocerebellar pathways. The dorsal and ventral spinocerebellar pathways carry information from the lower body (T6 and below). The rostral spinocerebellar tract and the cuneocerebellar tract carry information from the upper body (above T6). Polysynaptic indirect spinocerebellar pathways (spino-olivo-cerebellar and spino-reticulo-cerebellar tracts) also are present.

## Sensory Channels - Lemniscal

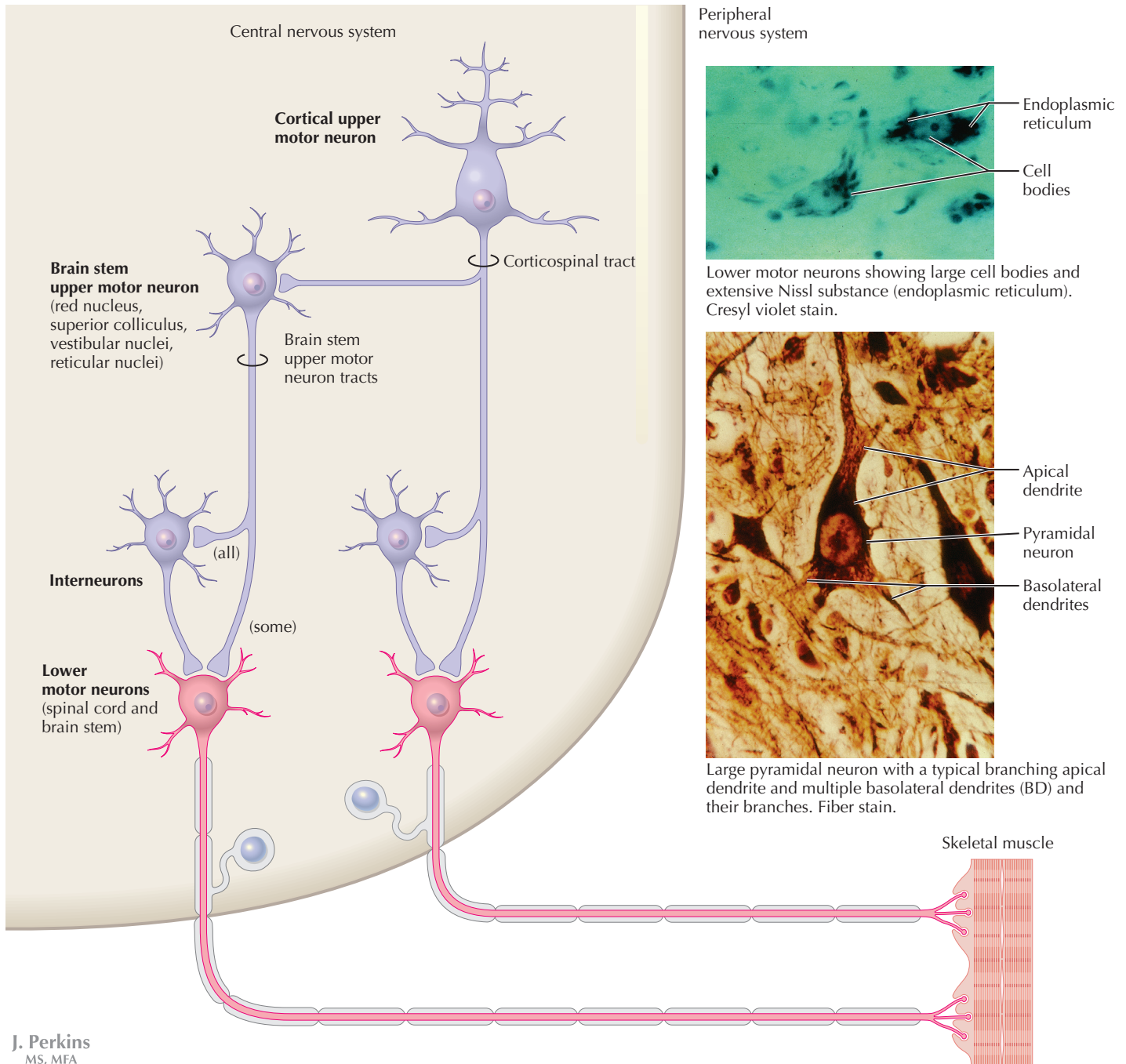


## 9.8 SENSORY CHANNELS: LEMNISCAL

Primary sensory axons carrying sensory information destined for conscious perception arise from receptors in superficial and deep tissue. These axons enter the CNS via the dorsal roots and terminate on secondary sensory nuclei in the spinal cord or brain stem. Secondary sensory axons from these nuclei cross the midline (decussate), ascend as lemniscal pathways, and terminate in the contralateral thalamus. These specific thalamic nuclei then project to specific regions of the primary sensory cortex, where fine-grained analysis of incoming, consciously perceived sensory information takes place. Somatosensory information is directed into two sets of channels, protopathic and epicritic. The epicritic information (fine, discriminative sensation; vibratory sensation; joint position sense) is transduced by primary sensory neurons (dorsal root ganglion cells) that send myelinated axons to neurons in the medulla; the nucleus gracilis (lower body, T6 and below); and the nucleus cuneatus (upper body, above T6). Nuclei gracilis and cuneatus give rise to the medial lemniscus, a crossed secondary sensory pathway that terminates in the ventral posterolateral (VPL) nucleus of the thalamus. This thalamic nucleus has reciprocal projections with cortical neurons in the postcentral gyrus (Brodmann's areas 3, 1, and 2). This entire epicritic somatosensory system is highly topographically orga-

nized, with each region of the body represented in each nucleus and axonal pathway. The protopathic information (pain, temperature sensation, light moving touch) is transduced by primary sensory neurons (dorsal root ganglion cells) that project mainly via small myelinated and unmyelinated axons to neurons in the dorsal horn of the spinal cord. These spinal cord neurons give rise to the spinothalamic tract (spinal lemniscus), a secondary sensory pathway that terminates in separate neuronal sites in the VPL nucleus of the thalamus. This portion of the VPL nucleus communicates mainly with the primary sensory cortex (SI) and a secondary area of somatosensory cortex (SII) posterior to the lateral postcentral gyrus. Some unmyelinated nociceptive protopathic axons that terminate in the dorsal horn of the spinal cord interconnect with a cascade of spinal cord interneurons that project mainly into the reticular formation of the brain stem (the spinoreticular pathway). This more diffuse pain system is processed through nonspecific thalamic nuclei with projections to somatosensory cortices and more widespread regions of cortex. This system can result in the perception of excruciating, long-lasting pain that may exceed the duration and intensity of direct peripheral stimuli. Chronic activation of this system can result in chronic neuropathic pain, persisting and reinforced by central mechanisms.

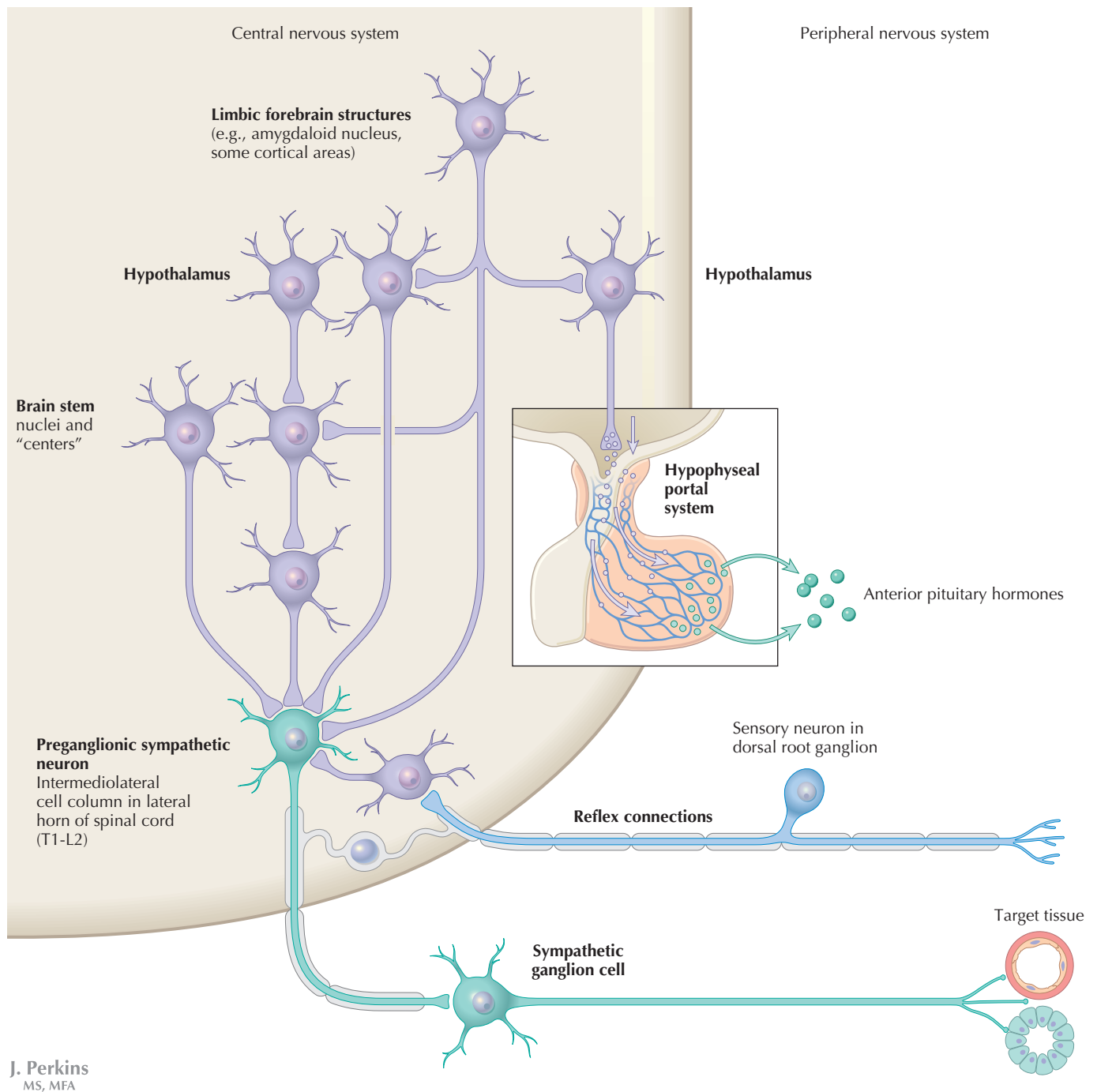




## 9.9 MOTOR CHANNELS: BASIC ORGANIZATION OF LOWER AND UPPER MOTOR NEURONS

LMNs are found in the anterior horn of the spinal cord and in motor cranial nerve nuclei in the brain stem. Their axons exit via the ventral roots or cranial nerves to supply skeletal muscles. LMN synapses with muscle fibers form neuromuscular junctions and release the neurotransmitter acetylcholine, which acts on nicotinic receptors on the skeletal muscle fibers. A motor unit consists of an LMN, its axon, and the muscle fibers the axon innervates. LMNs are regulated and

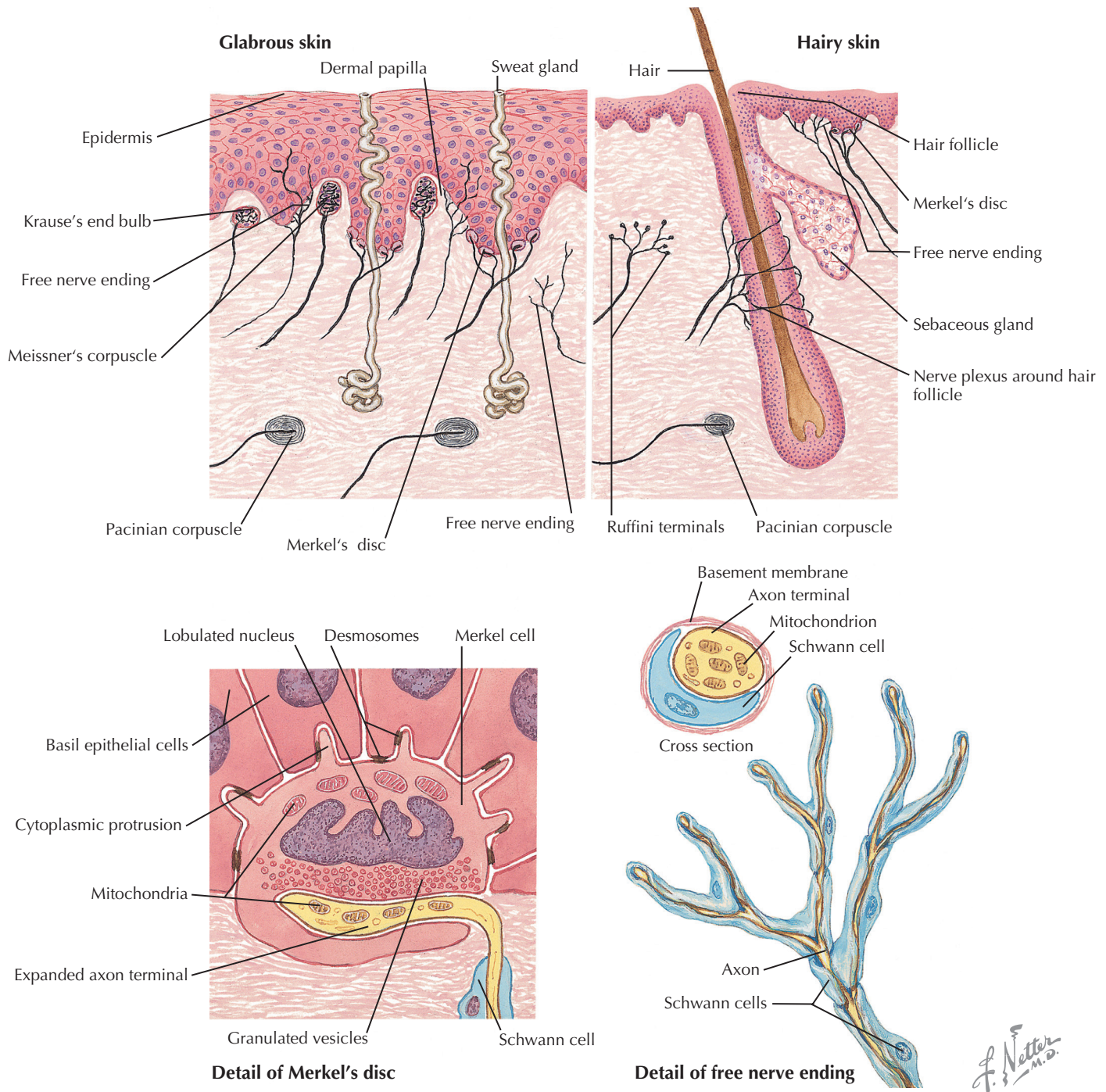
coordinated by groups of upper motor neurons (UMNs) found in the brain. Brain stem UMNs regulate basic tone and posture. Cortical UMNs (from corticospinal and corticobulbar tracts) regulate consciously directed, or volitional, movements. Cortical UMNs also have extensive connections with brain stem UMNs and may help to coordinate their activities. The cerebellum and basal ganglia aid in the coordination of movement and in pattern selection, respectively, via connections with UMNs; the cerebellum and basal ganglia do not connect with LMNs directly.



## 9.10 AUTONOMIC CHANNELS

Preganglionic neurons for the sympathetic nervous system (SNS) are found in the lateral horn (intermediolateral cell column) of the thoracolumbar (T1–L2) spinal cord (thoracolumbar system). Preganglionic neurons for the parasympathetic nervous system (PsNS) are found in nuclei of cranial nerves (CNs) III, VII, IX, and X and in the intermediate gray matter of the spinal cord between S2 and S4 (the craniosacral system). Preganglionic axons exit the CNS via cranial nerves or ventral roots and terminate in chain ganglia or collateral ganglia (the SNS) or in intramural ganglia in or near the organ innervated (the PsNS). Postganglionic autonomic axons innervate smooth muscle, cardiac muscle, secretory glands, metabolic cells (e.g., liver, fat cells), and cells of the immune

system. The SNS is a fight-or-flight system that responds to emergency demands. The PsNS is a homeostatic, reparative system active in more quiescent activities and in digestive and eliminative functions. Preganglionic responses are coordinated by autonomic UMN equivalents from the brain stem (autonomic centers), the hypothalamus, and the limbic forebrain structures. Inputs that affect visceral functions or elicit emotional responsiveness, originating from sensory inputs or from the brain (including the cerebral cortex), are conveyed through these central autonomic regulatory systems, which help to coordinate appropriate autonomic responses. These central autonomic regulatory systems coordinate autonomic responses that affect both visceral functions and neuroendocrine outflow from the pituitary gland.

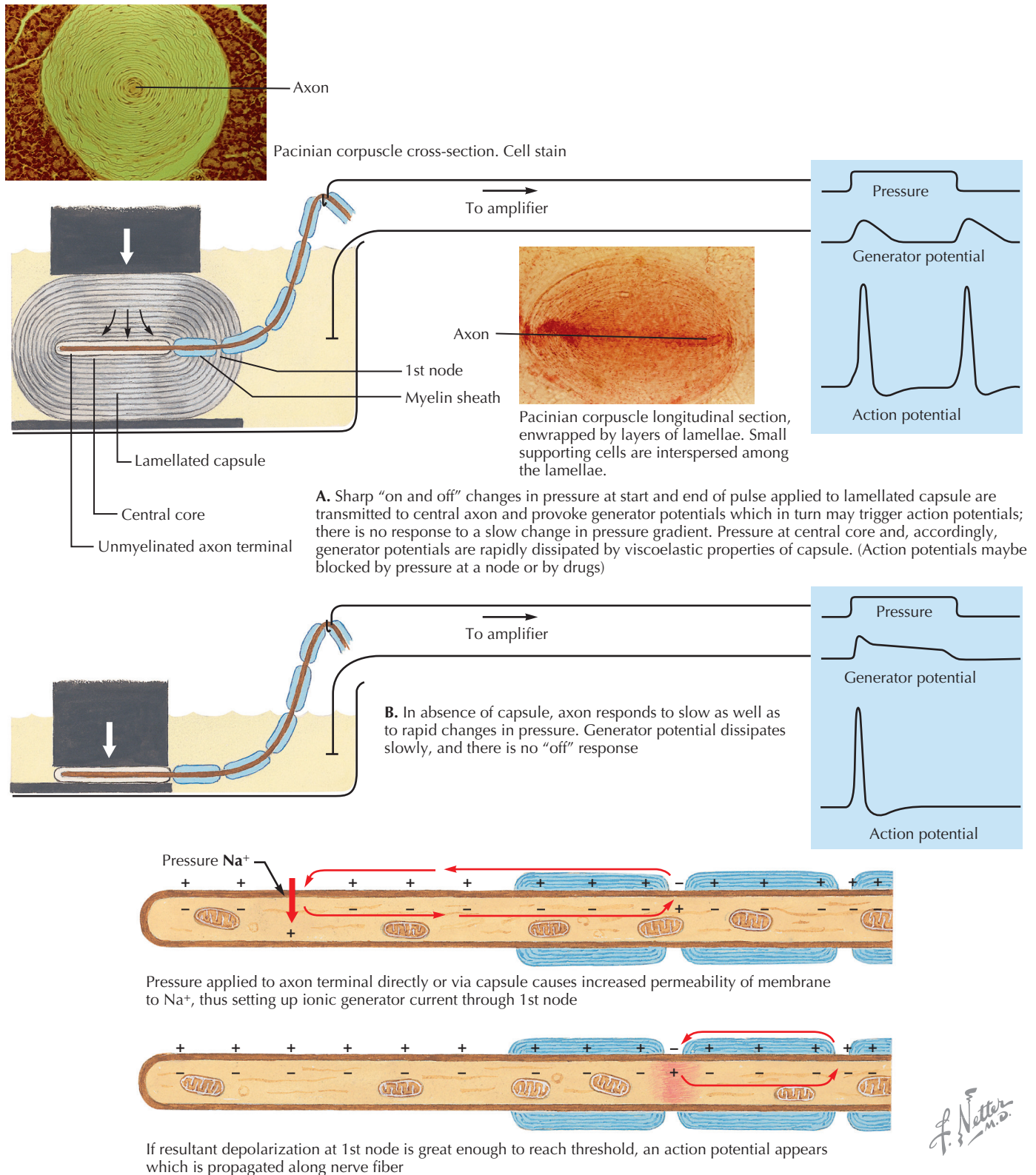


### 9.11 CUTANEOUS RECEPTORS

Cutaneous receptors are found at the distal ends of the primary sensory axon; they act as dendrites, in which threshold stimuli lead to the firing of an action potential at the initial segment of the primary sensory axon. Although specific types of sensory receptors are thought to code for consciously perceived modalities, there is not an exact correlation. Glabrous skin and hairy skin contain a wide variety of sensory receptors for detecting mechanical, thermal, or nociceptive (consciously perceived as painful) stimuli applied on the body surface. These receptors include bare nerve endings (nociception, thermal sensation)

and encapsulated endings. The latter include pacinian corpuscles (rapidly adapting mechanoreceptors for detecting vibration or brief touch); Merkel's discs (slowly adapting mechanoreceptors for detecting maintained deformation or sustained touch on the skin); Meissner's corpuscles (rapidly adapting mechanoreceptors for detecting moving touch); Ruffini endings (slowly adapting mechanoreceptors for detecting steady pressure applied to hairy skin); hair follicle receptors (rapidly adapting); and Krause end bulbs (possibly thermoreceptors). The initial segment of the primary sensory axon is immediately adjacent to the sensory receptor.

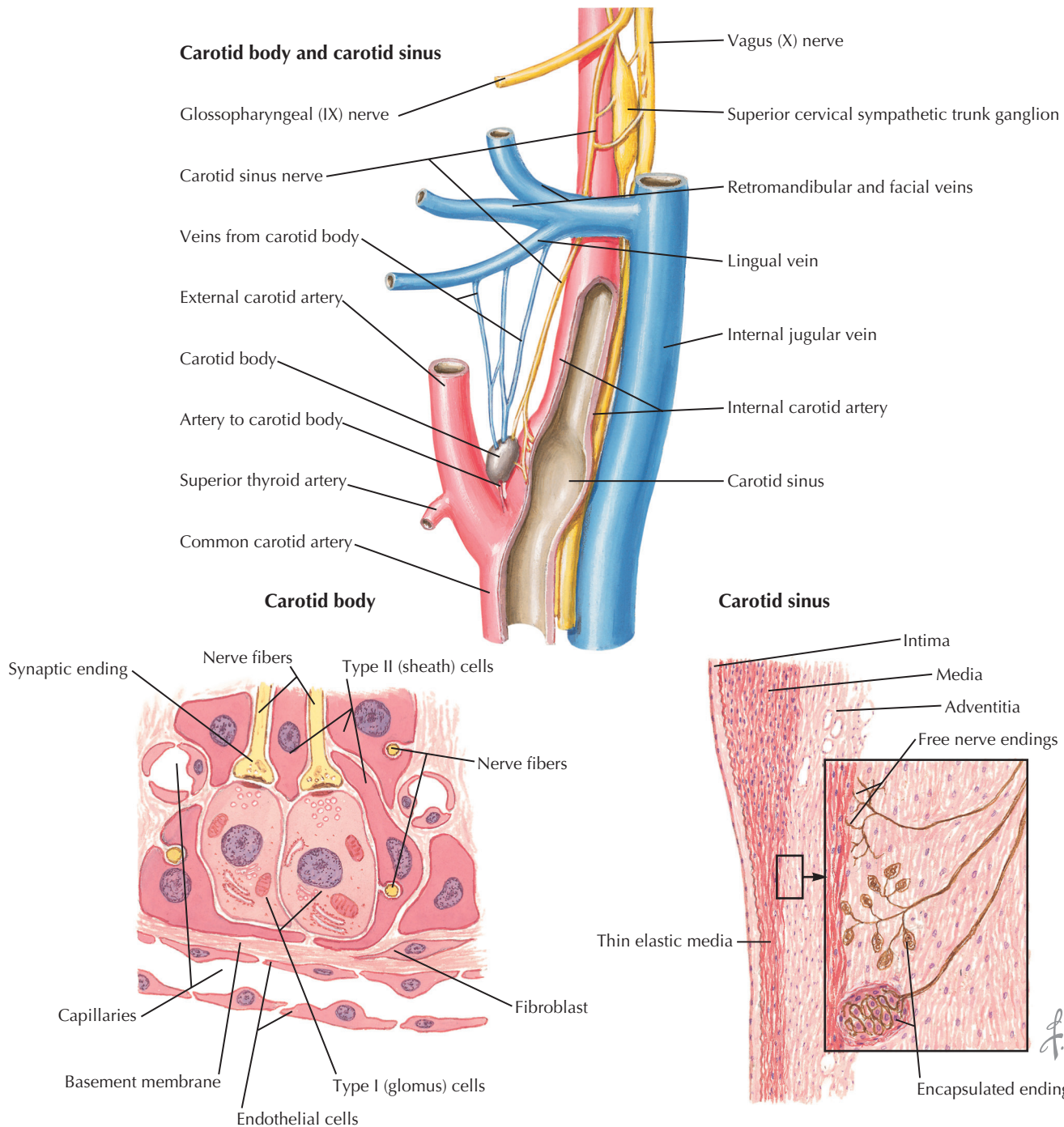




### 9.12 PACINIAN CORPUSCLES

Pacini corpuscles are mechanoreceptors that transform mechanical force or displacement into action potentials in large-diameter primary sensory axons. The mechanical stimulus is modified by the viscoelastic properties of the contributing lamellae of the pacinian corpuscle and the associated

accessory cells. An action potential results when a generator potential of sufficient magnitude to bring the initial segment of the axon to threshold is elicited. The onset and cessation of mechanical deformation enhance ionic permeability in the axon, optimizing the physiological response of the pacinian corpuscle to vibratory stimuli.

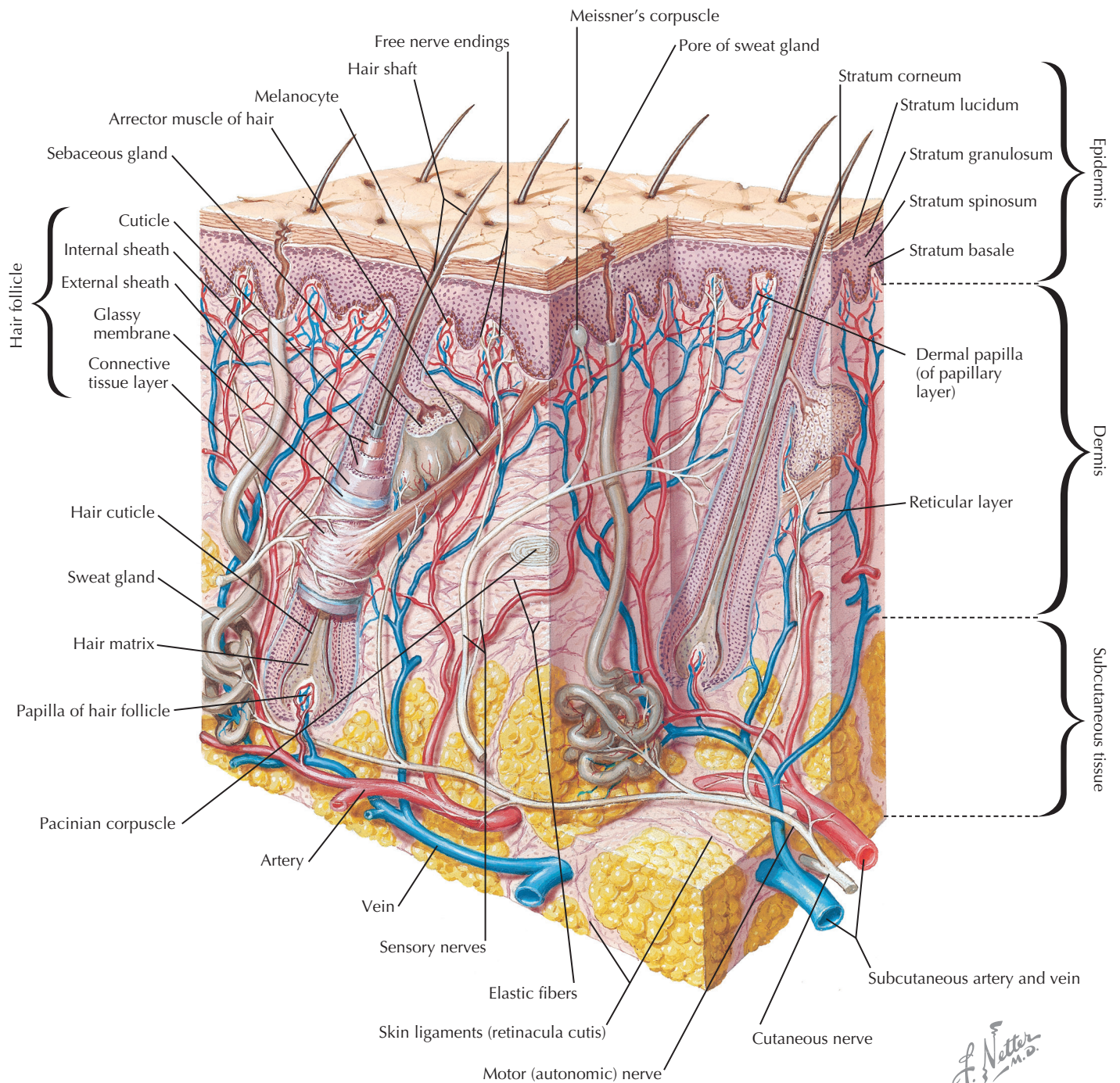


### 9.13 INTEROCEPTORS

Interoceptors, including internal nociceptors, chemoreceptors, and stretch receptors, inform the CNS about the internal state of the body. The carotid body, a specialized chemoreceptor for detecting carbon dioxide (in a hypoxic state) or to a lesser extent low blood pH resulting in increased respiration, is associated with afferent axons of CN IX that project to the

caudal nucleus solitarius in the medulla. The carotid sinus, a thin-walled region of the carotid artery, contains encapsulated and bare nerve endings that act as stretch receptors. These stretch receptors respond to increased arterial pressure as baroreceptors, send primary afferents to the caudal nucleus solitarius via CN IX, and elicit reflex bradycardia and decrease in blood pressure.



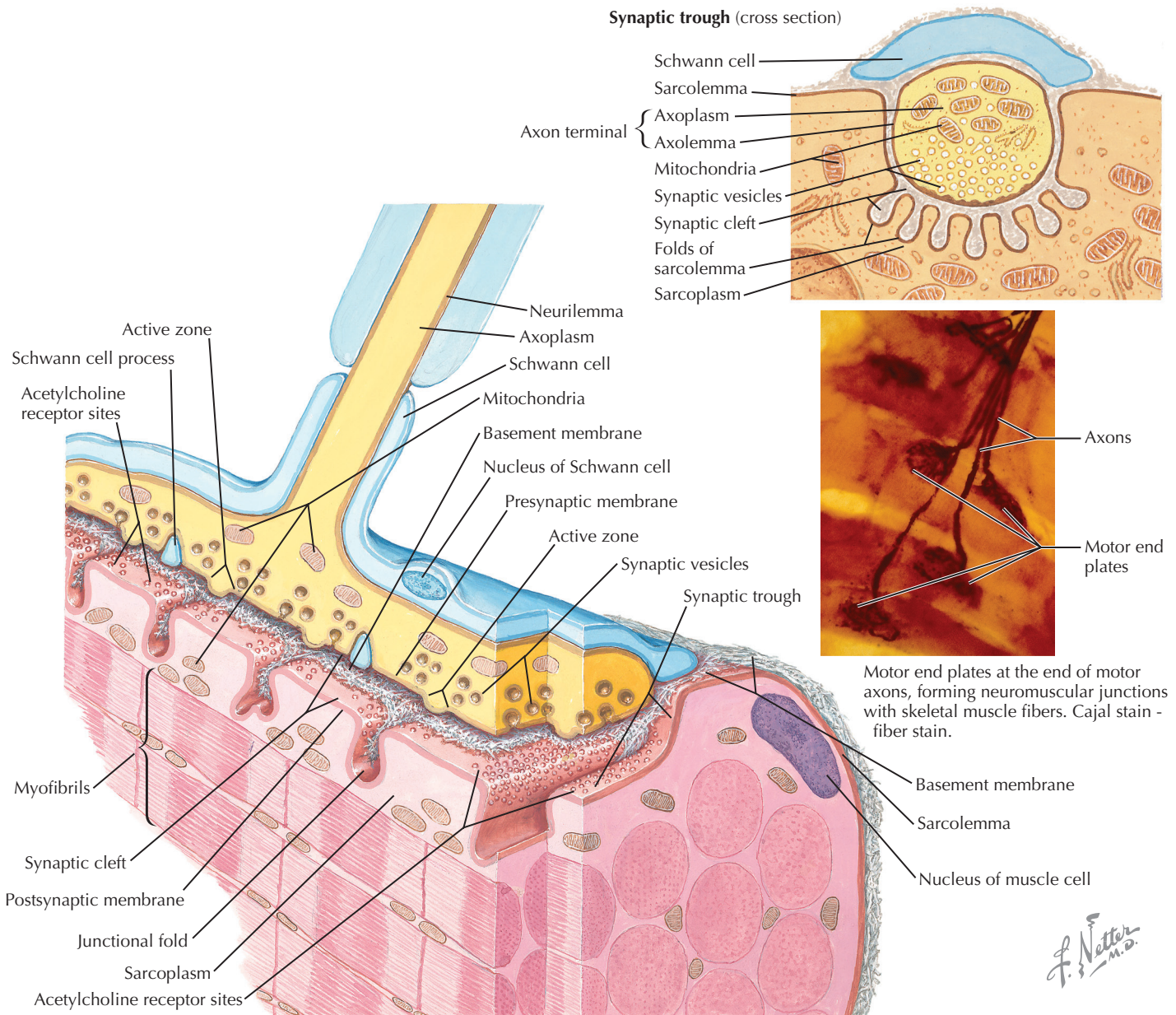


### 9.14 SKIN AND ITS NERVES

The skin is supplied with a variety of receptor types (see Fig. 9.11) that transduce slowly and rapidly adapting mechanical stimuli and deformation into electrical impulses in primary afferent fibers. The bare nerve endings are associated mainly with nociceptors, peripheral arborizations of unmyelinated axons. Some nociceptors and thermoreceptors are associated

with small myelinated axons. These axons collectively contribute somatosensory information to the spinothalamic/spinoreticular lemniscal system for protopathic sensation. The more complex encapsulated receptors contribute somatosensory information to the dorsal column/medial lemniscal system for epicritic sensation and are associated with larger myelinated axons.



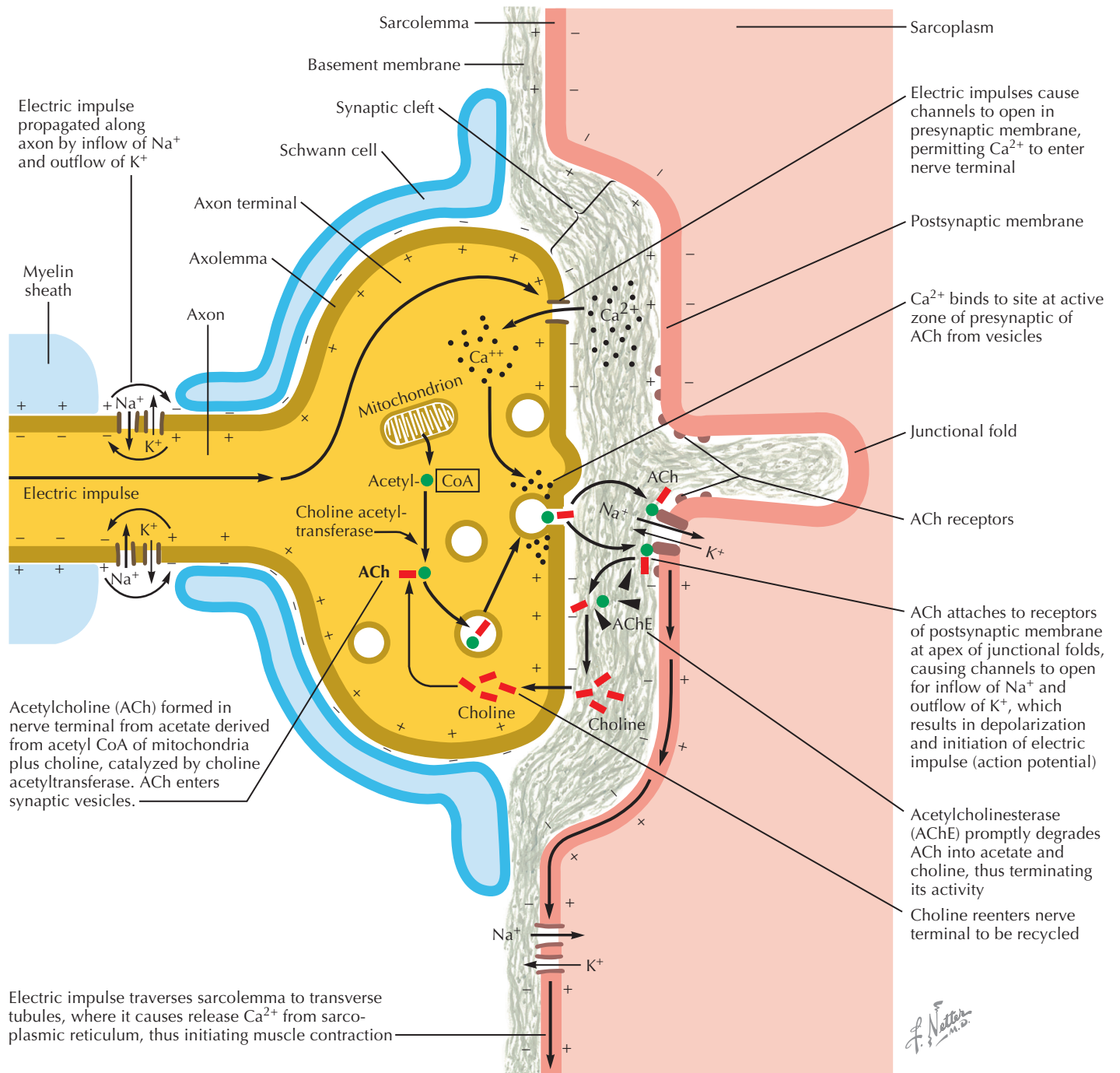


### 9.15 THE NEUROMUSCULAR JUNCTION AND NEUROTRANSMISSION

Axons of LMNs that synapse on skeletal muscle form expanded terminals called neuromuscular junctions (motor end plates). The motor axon loses its myelin sheath and expands into an extended terminal that resides in a trough in the muscle fiber and is covered by a layer of Schwann cell cytoplasm. The postsynaptic membrane is thrown into secondary folds. When an action potential invades the motor terminal, several hundred vesicles simultaneously release their acetylcholine (ACh) into the synaptic cleft. The ACh binds to nicotinic receptors on the muscle sarcolemma, initiating a motor end-plate potential, which is normally of sufficient magnitude to result in the firing of a muscle action potential, leading to contraction of the muscle fiber. A single muscle fiber has only one neuromuscular junction, but a motor axon may innervate multiple muscle fibers.

#### CLINICAL POINT

An action potential that invades the motor end plate results in a calcium-mediated simultaneous release of multiple quanta (vesicles) of ACh. This released ACh acts on nicotinic cholinergic receptors on the postjunctional membrane, normally resulting in a muscle contraction (excitation-contraction coupling). In myasthenia gravis, antibodies against the cholinergic nicotinic receptors greatly reduce the number of active receptors available for stimulation by released ACh. The size and number of ACh quanta appear to be normal. As a consequence, there is easy fatigability of involved muscles with repeated attempts at contraction. Ocular, facial, and bulbar muscles are the most likely to be affected by this disease, with resultant ptosis, drooping face, diplopia with strabismus, and dysarthria, dysphonia, and dysphagia. Limb muscles (mainly proximal) are involved only in advanced myasthenia gravis. The muscles do not show wasting and atrophy because they are not denervated; muscle stretch reflexes are elicitable.

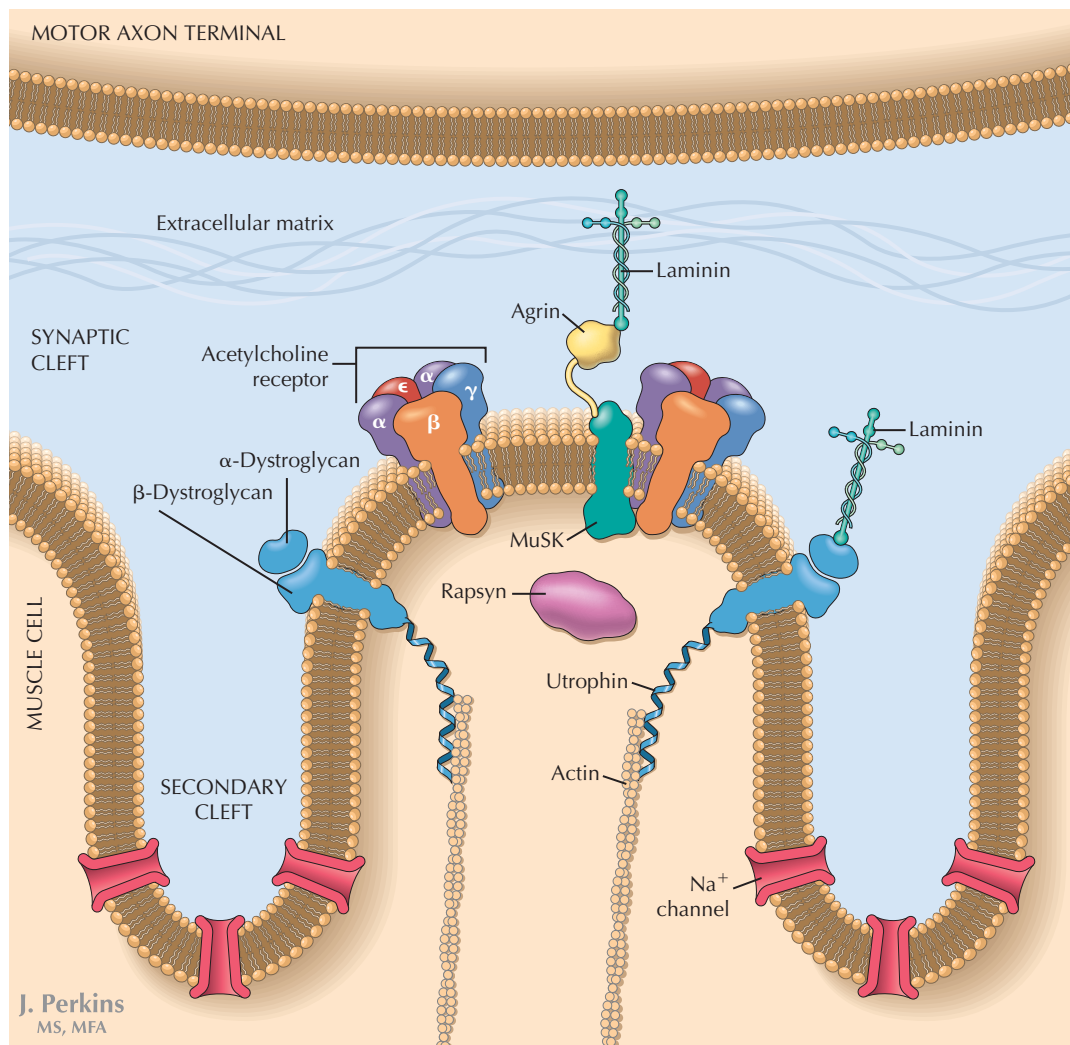


### 9.16 PHYSIOLOGY OF THE NEUROMUSCULAR JUNCTION

Mechanisms by which a motor action potential initiates the release of acetylcholine, activating nicotinic cholinergic recep-

tors on the muscle membrane, initiating muscle contraction. This process is called excitation-contraction coupling.





Representation of the normal neuromuscular junction, adult acetylcholine receptor in the postsynaptic muscle membrane and other important associated proteins

### 9.17 MAJOR STRUCTURES AND PROTEINS IN THE NORMAL NEUROMUSCULAR JUNCTION

Motor axons innervate skeletal muscle fibers through a series of interactions that include the nerve traveling along a laminin substrate, an important trimeric protein family helping to establish the basal lamina of the basement membrane of the neuromuscular junction (NMJ). Muscle-specific kinase (MuSK) is a receptor tyrosine kinase that is required to form the NMJ; it signals through casein kinase 2 (CK2), Dok-7, and rapsyn to form and maintain the NMJ and to orchestrate clustering of ACh receptors (AChRs) at the NMJ. Agrin, a glycoprotein secreted by the growing end of the motor axon, binds to MuSK and aids in this process. Laminin- $\alpha 4$  acts as a presynaptic organizer and binds to agrin, which acts as a postsynaptic organizer. These molecules are necessary to maintain the appositions of the presynaptic and postsynaptic specializations of the NMJ.

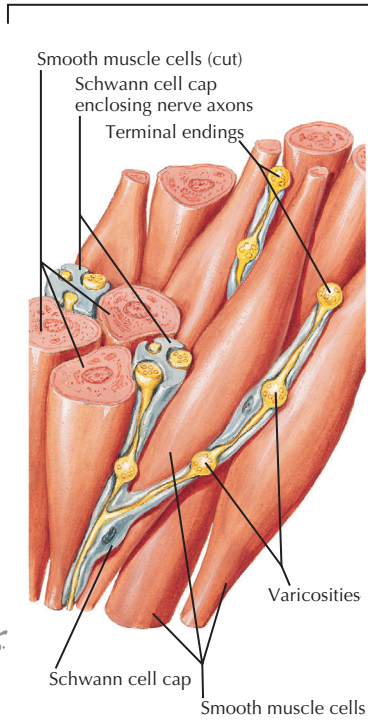
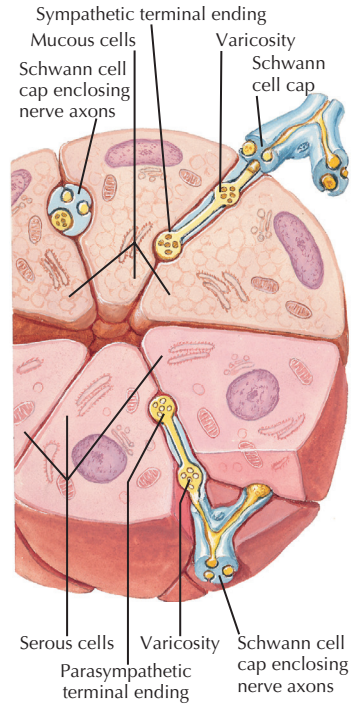
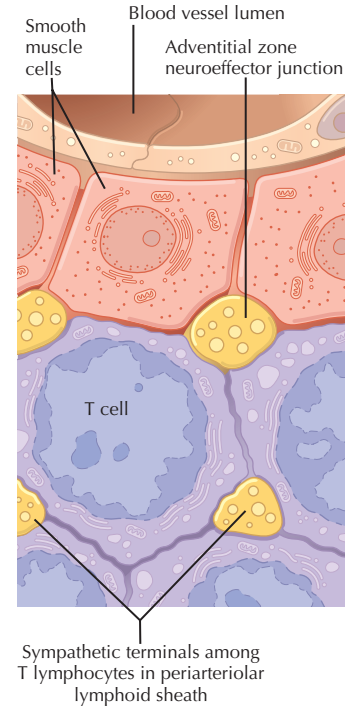
Utrophin forms a link between the extracellular matrix and the thin helical filaments of F-actin, part of the contractile machinery of the muscle fiber, along with myosin, and helps keep the actin filaments from depolymerizing. Utrophin and dystroglycans (dystrophin-associated glycoproteins), which

also bind to the F-actin filaments, also serve as an agrin receptor and aid in the clustering of AChRs at the postsynaptic site of the NMJ.

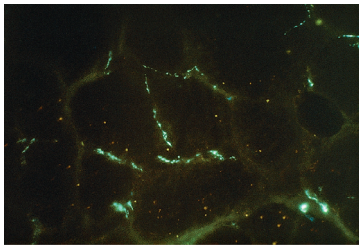
#### CLINICAL POINT

Muscular dystrophies (MD) are genetic muscular disorders characterized by progressive skeletal muscle weakness and dysfunction, defects in muscle proteins (e.g., dystrophins), and associated physiologic and anatomic problems such as scoliosis. There are multiple forms of muscular dystrophy. Duchenne's muscular dystrophy, the most common form of MD in children, affecting mainly males, is a recessive mutation of the dystrophin gene on the short arm of the X chromosome affecting skeletal muscle and some other structures (GI system, brain, heart, endocrine system). The cytoskeleton of muscles is impaired because of the absence of dystrophin and dystrophin-related complexes. Muscle wasting occurs, often in the presence of the accumulation of fat and fibrous connective tissue (pseudohypertrophy). Muscle weakness can be accompanied by heart and respiratory failure. Standard therapy is occupational therapy and physiotherapy. However, a new approach involving molecular therapy is currently being explored. Antisense oligonucleotides (AONs) have been designed that bind to the complementary sequences of mRNA, skipping the affected exon, and inducing partially functional isoforms of dystrophin in skeletal muscles. Before widespread use of AONs occurs, further refinement of delivery and effectiveness of this treatment are needed.

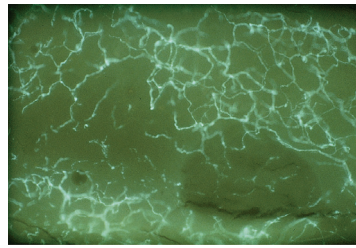


**A. Smooth muscle****B. Gland (submandibular)****C. Lymphoid tissue (spleen)**

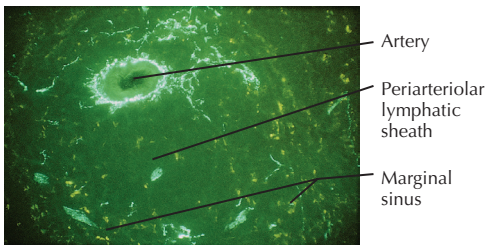
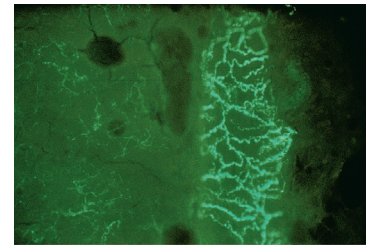
*J. Netter M.D.*  
with  
J. Perkins  
MS, MFA



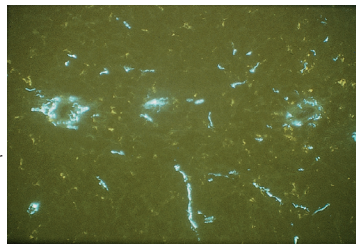
**D.** Noradrenergic (NA) postganglionic sympathetic nerve fibers supplying thoracic fat cells near the thymus. Glyoxylic acid fluorescence histochemistry (9.18 D-I). Nerve fibers and terminals appear turquoise.



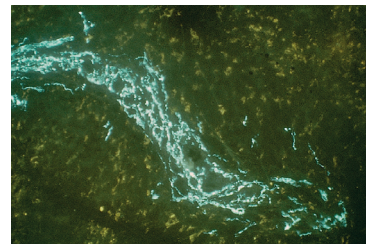
**E.** NA postganglionic sympathetic nerve fibers supplying the submandibular gland and its duct (**F**).



**G.** NA postganglionic sympathetic nerve fibers surrounding the central white pulp, shown in cross-sectional view, and fibers also present among T lymphocytes in the periarteriolar lymphatic sheath and along arrays of antigen-presenting cells along the marginal sinus.



**H.** NA nerve fibers in the splenic white pulp (see **G**), showing the central artery in a longitudinal expanse.

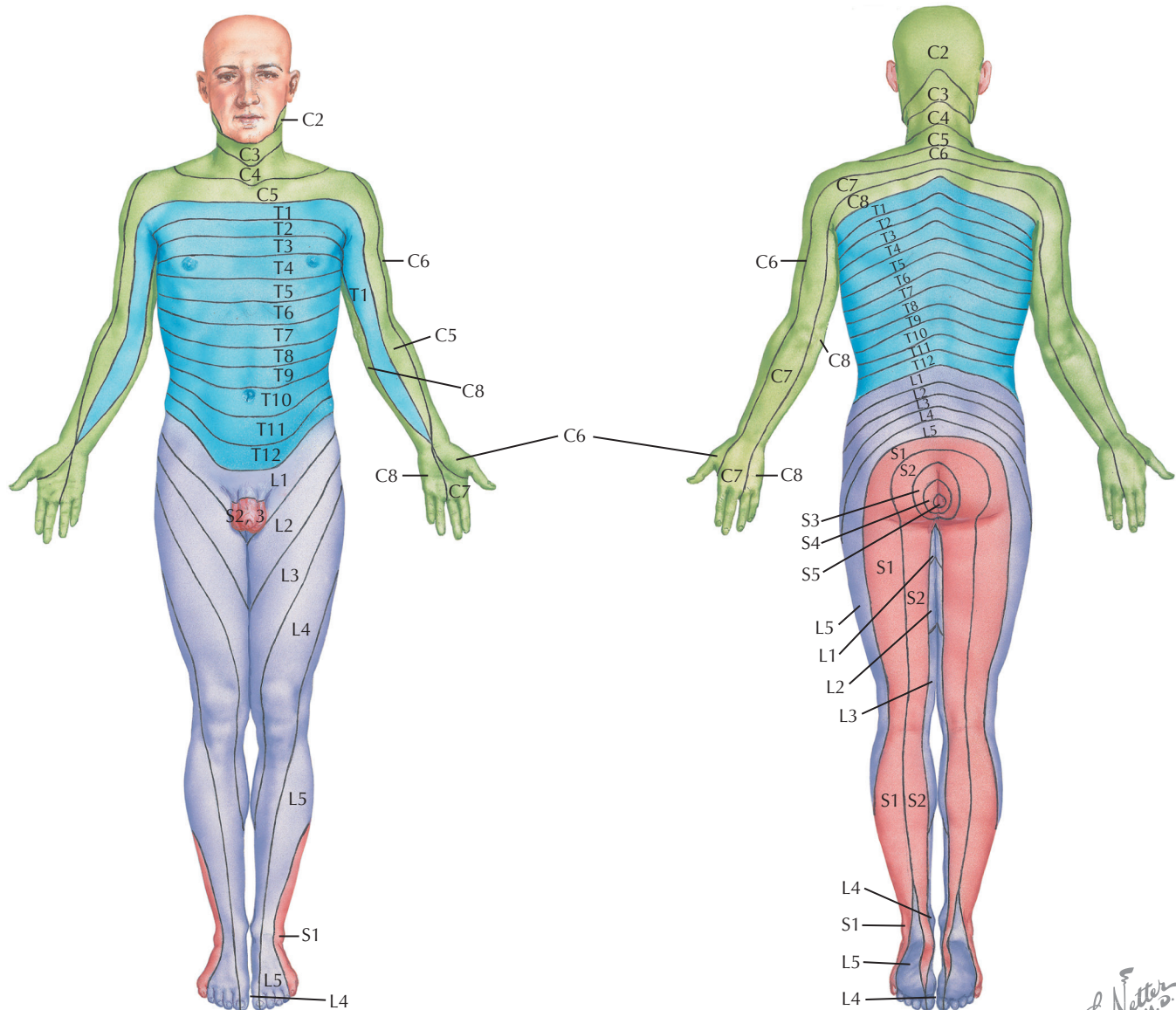


**I.** NA nerve fibers in the splenic white pulp (see **H**) in an experimental setting in which a mouse was treated with a high dose of cyclophosphamide, which temporarily mobilizes T lymphocytes and other immunocytes to leave the spleen, significantly diminishing the cellularity of the white pulp. The NA nerve fibers accommodate to the changing structure and cellularity of the splenic white pulp, and remain associated with the same compartments, with the consequence of greater density of nerve terminals, and more compact distribution in the white pulp. With recovery from the treatment and repopulation of the white pulp, the appearance of NA terminals, and their distribution and density, return to the normal picture (**H**).

## 9.18 NEUROEFFECTOR JUNCTIONS

Autonomic postganglionic axons form neuroeffector junctions with cardiac muscle, smooth muscle (**A**), secretory glands (**B**), metabolic cells such as hepatocytes and fat cells, and cells of the immune system (**C**). These nerve endings use mainly norepinephrine for the SNS and acetylcholine for the PsNS. These endings do not form classic CNS or motor end-plate synapses; instead, they terminate as neuroeffector junctions, releasing neurotransmitter into interstitial spaces. This

permits a widespread diffusion of the neurotransmitter as a paracrine secretion, initiating postsynaptic responses on cells with appropriate receptors (including many types of cells of the immune system). Some close appositions also are found, such as SNS endings on lymphocytes. Not all smooth muscle cells are innervated by neuroeffector junctions; they are coupled by gap junctions and can contract together when the innervated smooth muscle cell contracts.



#### Levels of Principal Dermatomes

<b>C5</b>	Clavicles
<b>C5, 6, 7</b>	Lateral parts of upper limbs
<b>C8; T1</b>	Medial sides of upper limbs
<b>C6</b>	Thumb
<b>C6, 7, 8</b>	Hand
<b>C8</b>	Ring and little fingers
<b>T4</b>	Level of nipples

<b>T10</b>	Level of umbilicus
<b>T12</b>	Inguinal or groin regions
<b>L1, 2, 3, 4</b>	Anterior and inner surfaces of lower limbs
<b>L4, 5; S1</b>	Foot
<b>L4</b>	Medial side of great toe
<b>L5; S1, 2</b>	Outer and posterior sides of lower limbs
<b>S1</b>	Lateral margin of foot and little toe
<b>S2, 3, 4</b>	Perineum

*F. Netter M.D.*

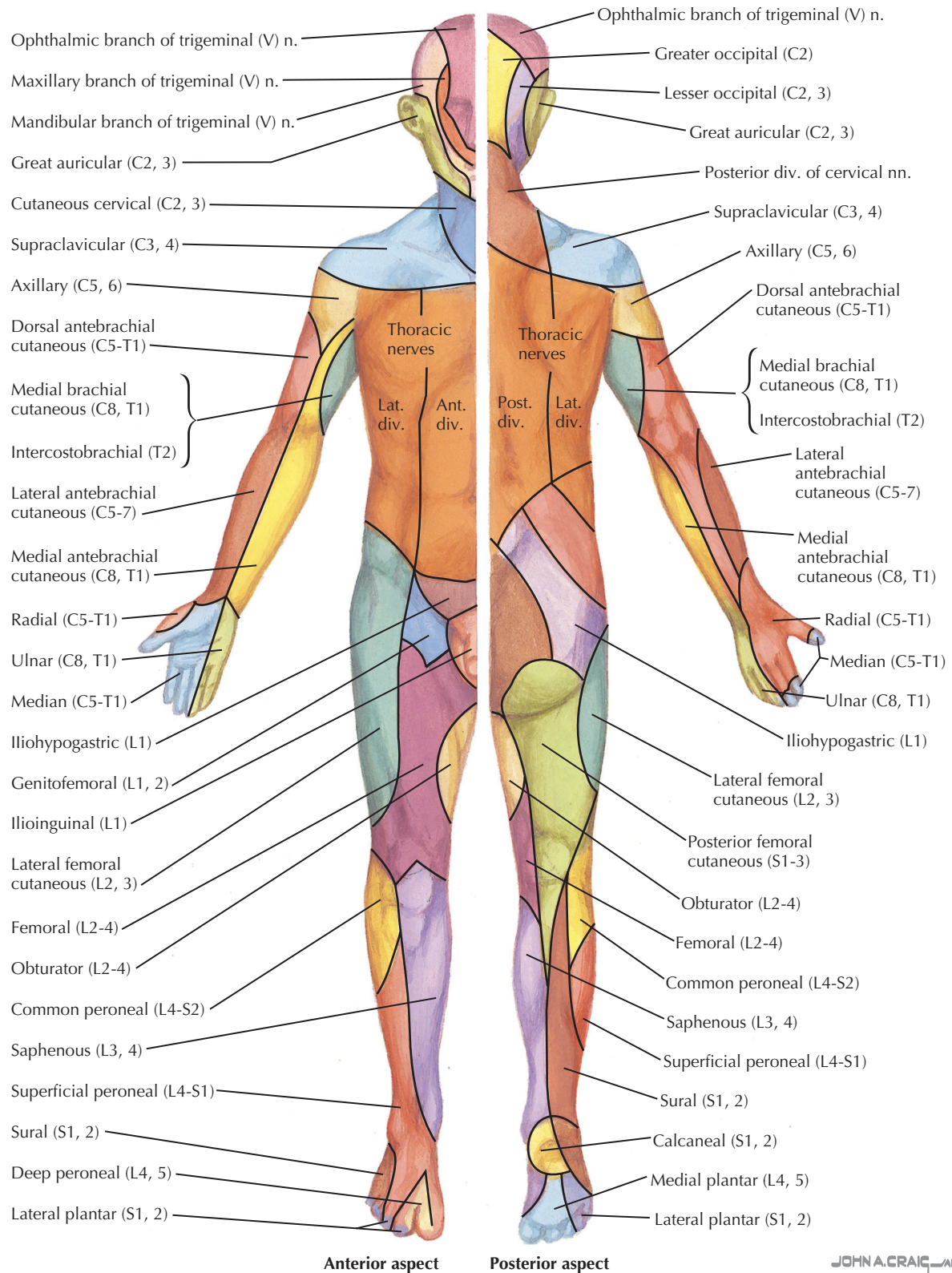
## SOMATIC NERVOUS SYSTEM

### 9.19 DERMATOMAL DISTRIBUTION

A dermatome is the cutaneous area supplied by a single spinal nerve root; the cell bodies are located in dorsal root ganglia. The spinal nerve roots are distributed to structures according to their associations with spinal cord segments. The nerve roots supplying neighboring dermatomes overlap. Thus, sectioning or dysfunction of a single dorsal root produces hypesthesia (diminished sensation), not anesthesia (total loss of sensation) in the region supplied predominantly by that dermatome, as shown in the figure. Dermatomal anesthesia requires damage to at least three dorsal roots: the central dorsal root and the roots above and below it. In contrast, an

irritative lesion such as a herniated intervertebral disc may produce sharp, radiating pain within the distribution of the affected dermatome. As the limb buds for the lower extremities develop, they draw out the nerve roots that correspond with their mesodermal cores and ectodermal coverings. The developing lower limbs rotate medially around a longitudinal axis, with a resultant oblique orientation of the dermatomes. The L1 and L2 dermatomes can be found in sites adjacent to S2 and S3 dermatomes because of the intervening segments migrating into more distal parts of the lower limbs. Knowledge of dermatomes is important for localizing peripheral nerve root lesions and distinguishing them from peripheral nerve lesions.



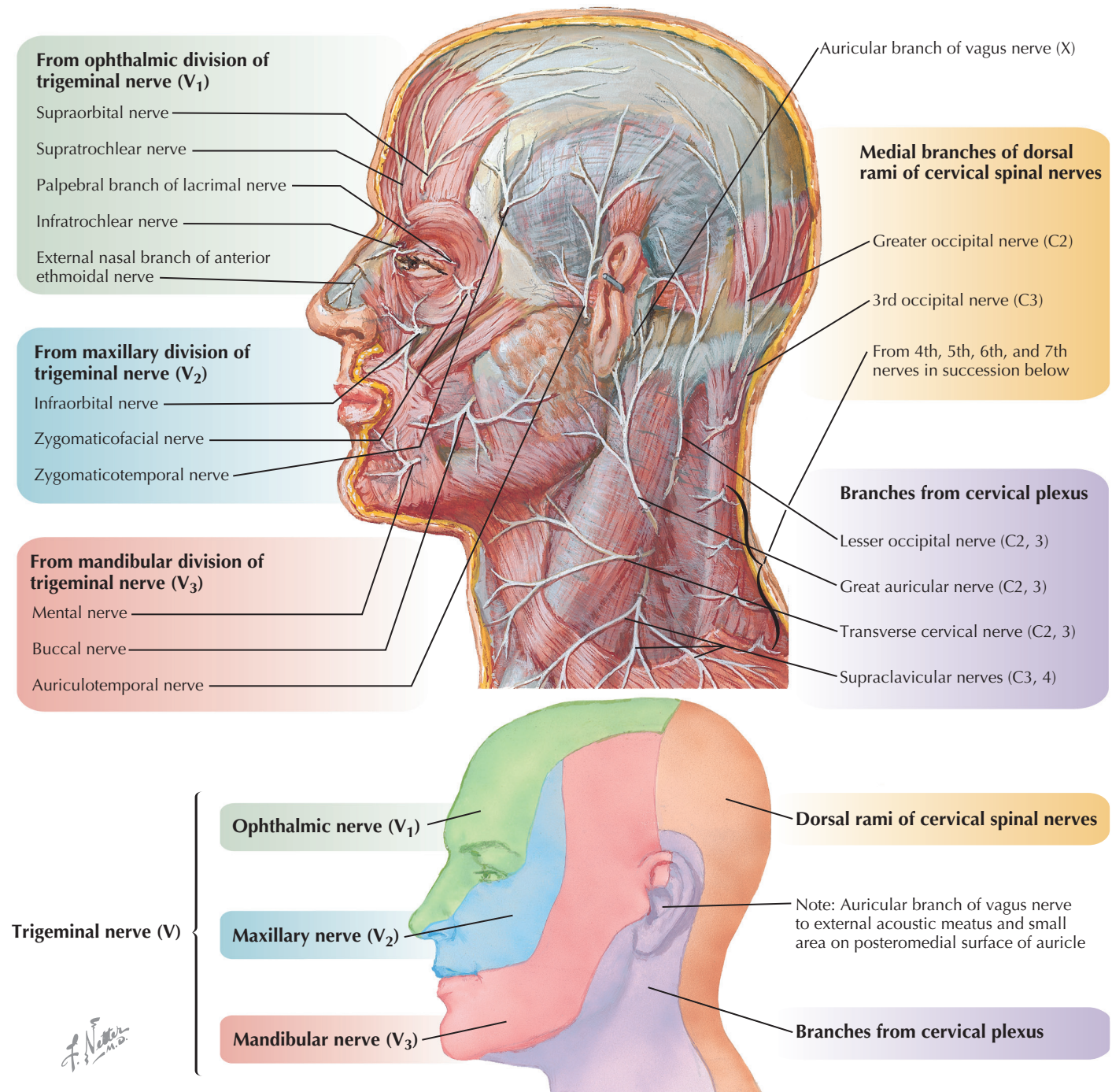


## 9.20 CUTANEOUS DISTRIBUTION OF PERIPHERAL NERVES

Peripheral nerves distribute sensory processes and endings to specific surface regions of the body. These sites may be inner-

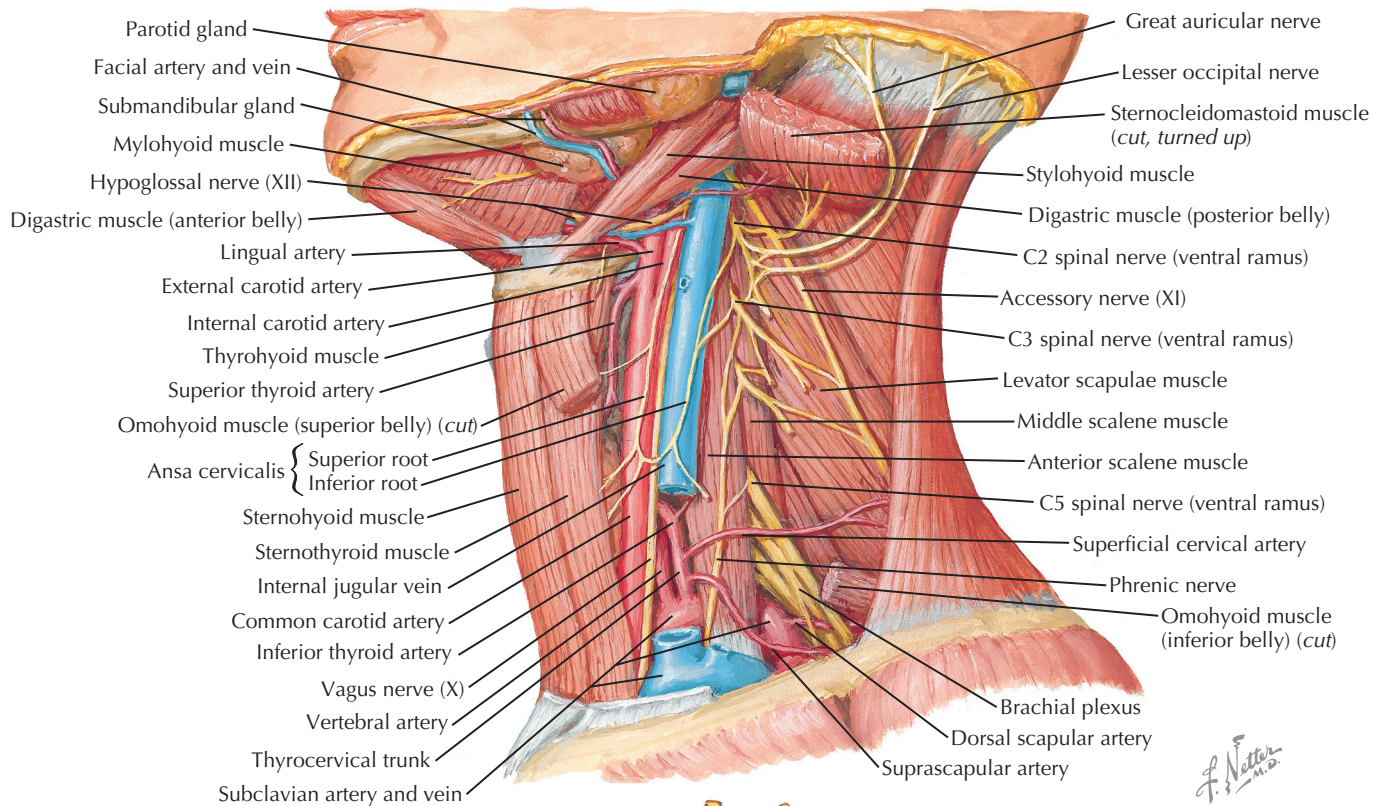
vated by a nerve with contributions from several dermatomes. A nerve lesion can leave the site of cutaneous distribution devoid of all sensation (anesthetic). Sites of innervation by specific nerves vary from person to person.





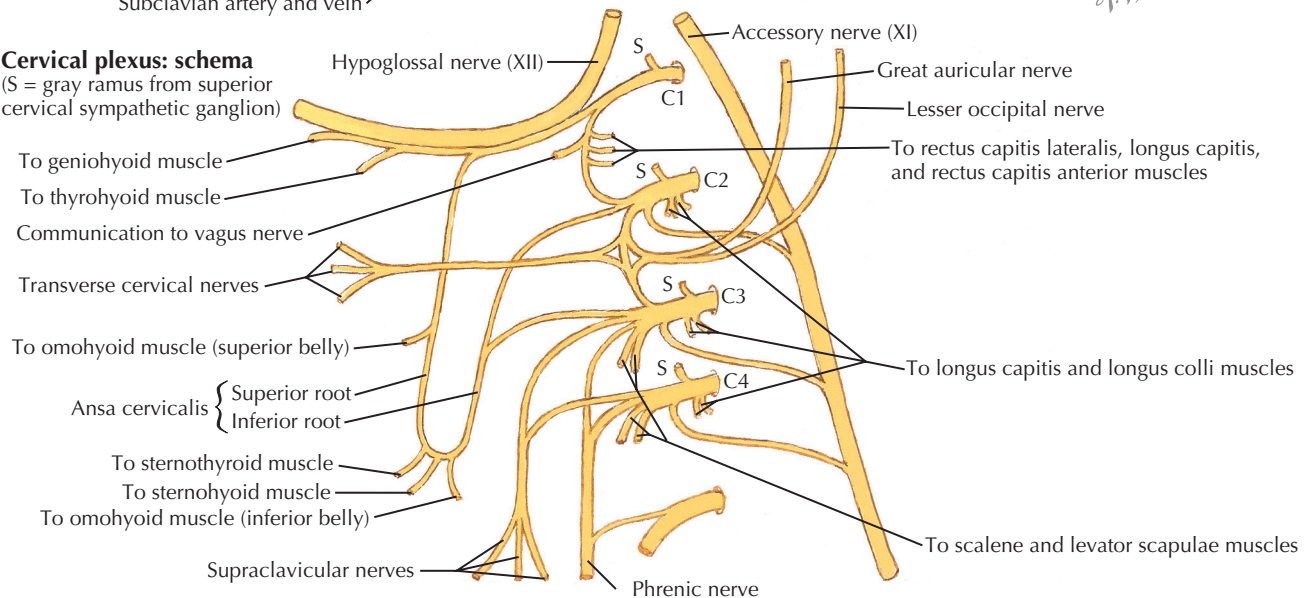
## 9.21 CUTANEOUS NERVES OF THE HEAD AND NECK

Cutaneous nerves of the head and neck derive from dorsal rami of cervical spinal nerves, from branches from the cervical plexus, and from all three divisions of the trigeminal nerve (CN V).



### Cervical plexus: schema

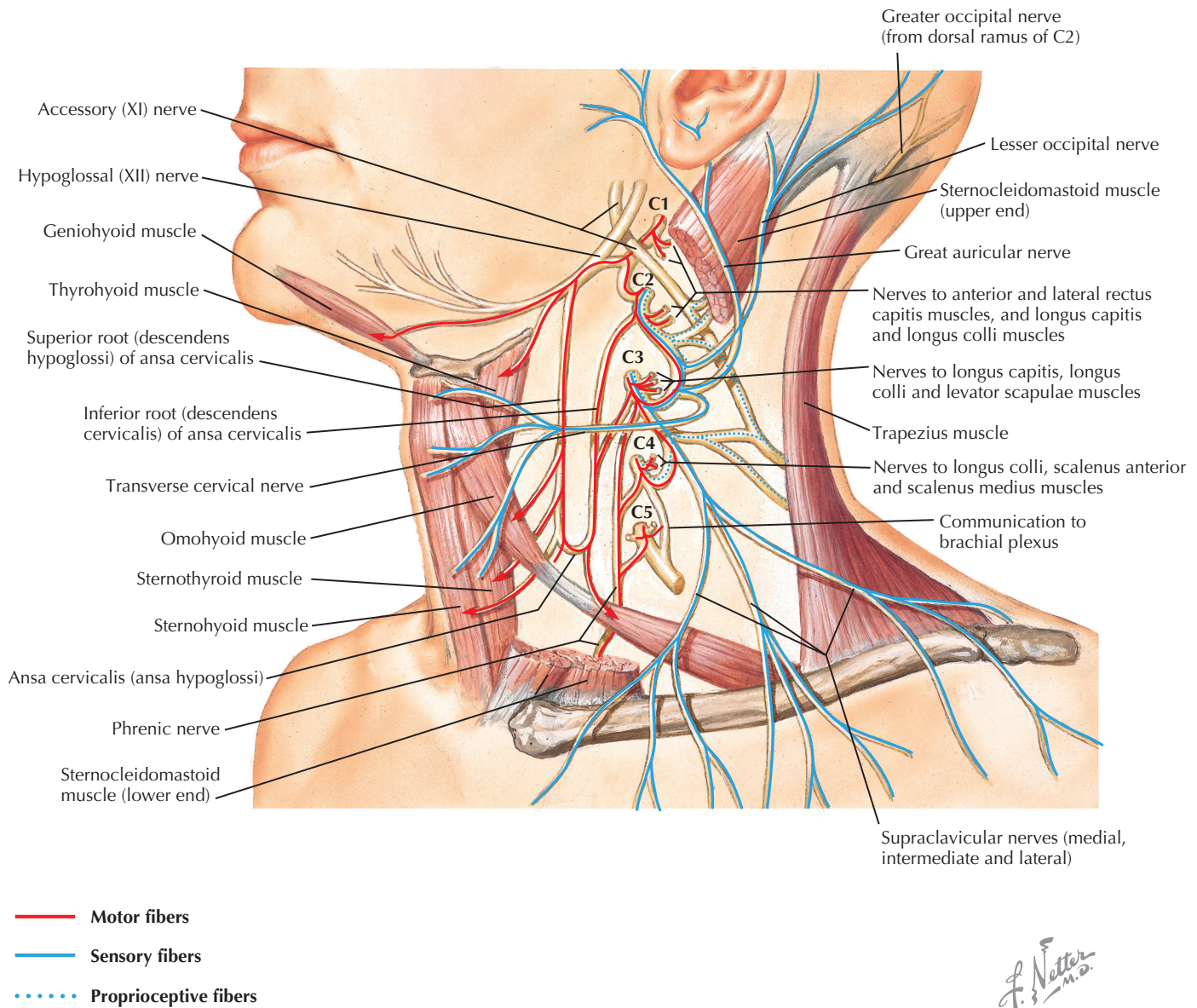
(S = gray ramus from superior cervical sympathetic ganglion)



## 9.22 CERVICAL PLEXUS IN SITU

This diagram of the cervical plexus in situ and the schema below demonstrate the distribution of branches from the C1–C4 nerve roots into the associated peripheral nerves and branches to the innervated muscles.





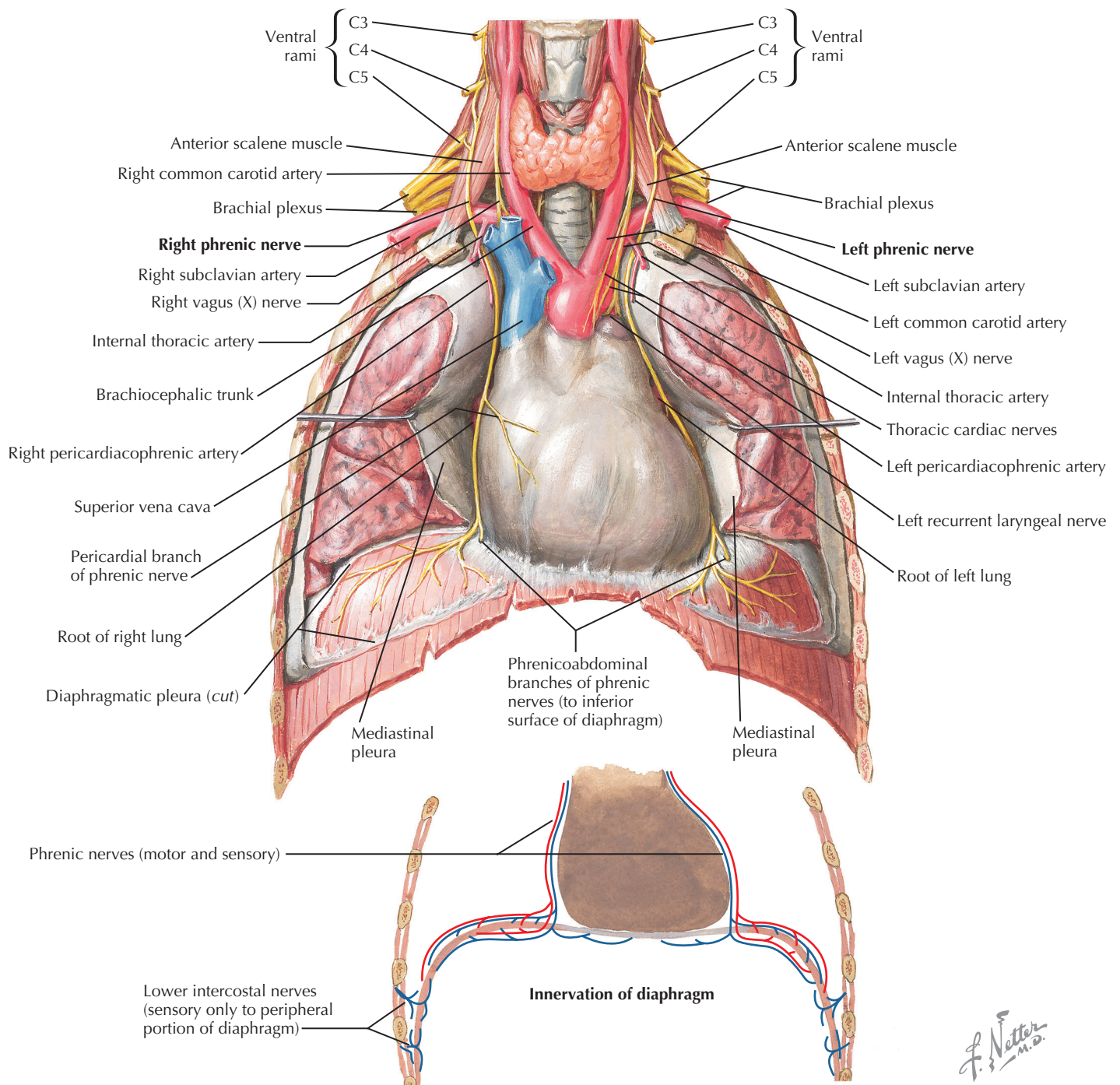
### 9.23 CERVICAL PLEXUS

The cervical plexus lies deep to the sternocleidomastoid muscle. Its branches convey motor fibers to many cervical muscles and to the diaphragm. Its sensory fibers convey exteroceptive information from parts of the scalp, neck, and chest as well as proprioceptive information from muscles, tendons, and joints. Sympathetic sudomotor and vasomotor fibers travel with this plexus to blood vessels and glands. The superficial branches perforate the cervical fascia to supply cutaneous structures; the deep branches supply mainly muscles and joints.

#### CLINICAL POINT

The cervical plexus is formed from the anterior primary rami of C1–C4, deep to the sternocleidomastoid muscle and in front of the scalenus medius and levator scapulae muscles. Sensory branches include the greater and lesser occipital nerves, great auricular nerve, cutaneous cervical nerves, and supraclavicular nerves. The motor branches include the ansa hypoglossi, branches to scalenus medius and levator scapulae muscles, the phrenic nerve, and branches to the spinal accessory nerve. Lesions of the cervical plexus are uncommon, usually resulting from trauma, mass lesions, or as sequelae to surgery such as carotid endarterectomy. Involvement of motor branches results in disruption of muscular function, such as shoulder elevation and head rotation and flexion with spinal accessory nerve damage. Involvement of sensory branches results in loss of cutaneous sensation or in pain and paresthesias in regions of the head or neck supplied by these branches.



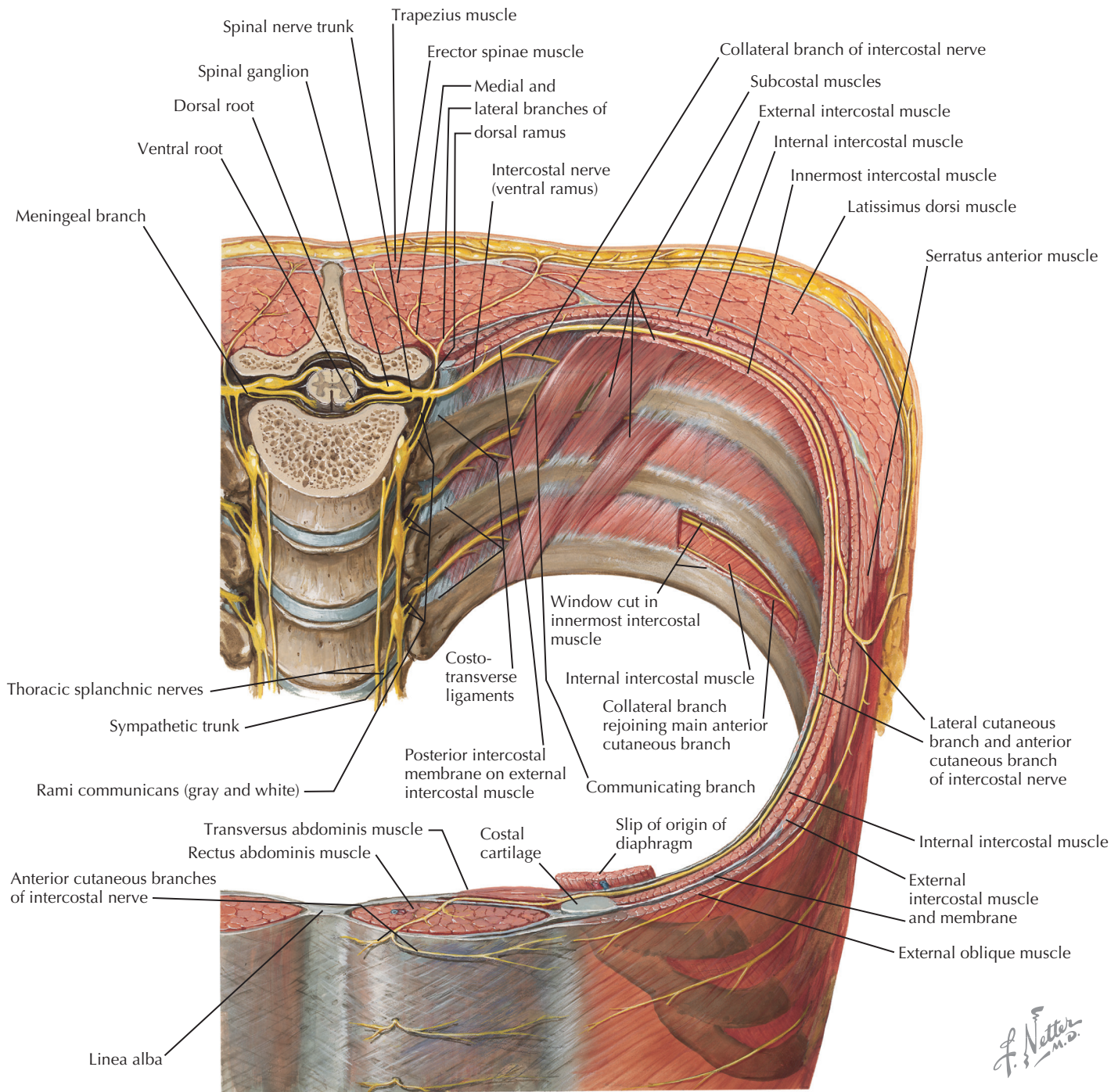


## 9.24 PHRENIC NERVE

The left and right phrenic nerves are the motor nerves that supply both sides of the diaphragm from the C3, C4, and C5 ventral roots. The phrenic nerve also contains many sensory nerve fibers that supply the fibrous pericardium, the mediastinal pleura, and central areas of the diaphragmatic pleura. Sympathetic postganglionic nerve fibers also travel with this nerve. Coordinated contraction of the diaphragm relies on central control of firing of LMNs through dendrite bundles in the spinal cord.

### CLINICAL POINT

The phrenic nerves derive from the C3–C5 ventral roots and provide the motor supply to the diaphragm. Lesions of the phrenic nerve usually occur in the mediastinum, not the cervical plexus. Pathological processes, such as enlarged mediastinal nodes, aortic aneurysms, mediastinal tumors, sequelae of surgery, and demyelination from Guillain-Barré syndrome, can damage these nerves. Unilateral damage to the phrenic nerve results in paralysis of the diaphragm on the ipsilateral side, which can usually be tolerated at rest but not following exertion. Bilateral phrenic nerve damage results in diaphragmatic paralysis with extreme dyspnea and hypoventilation.

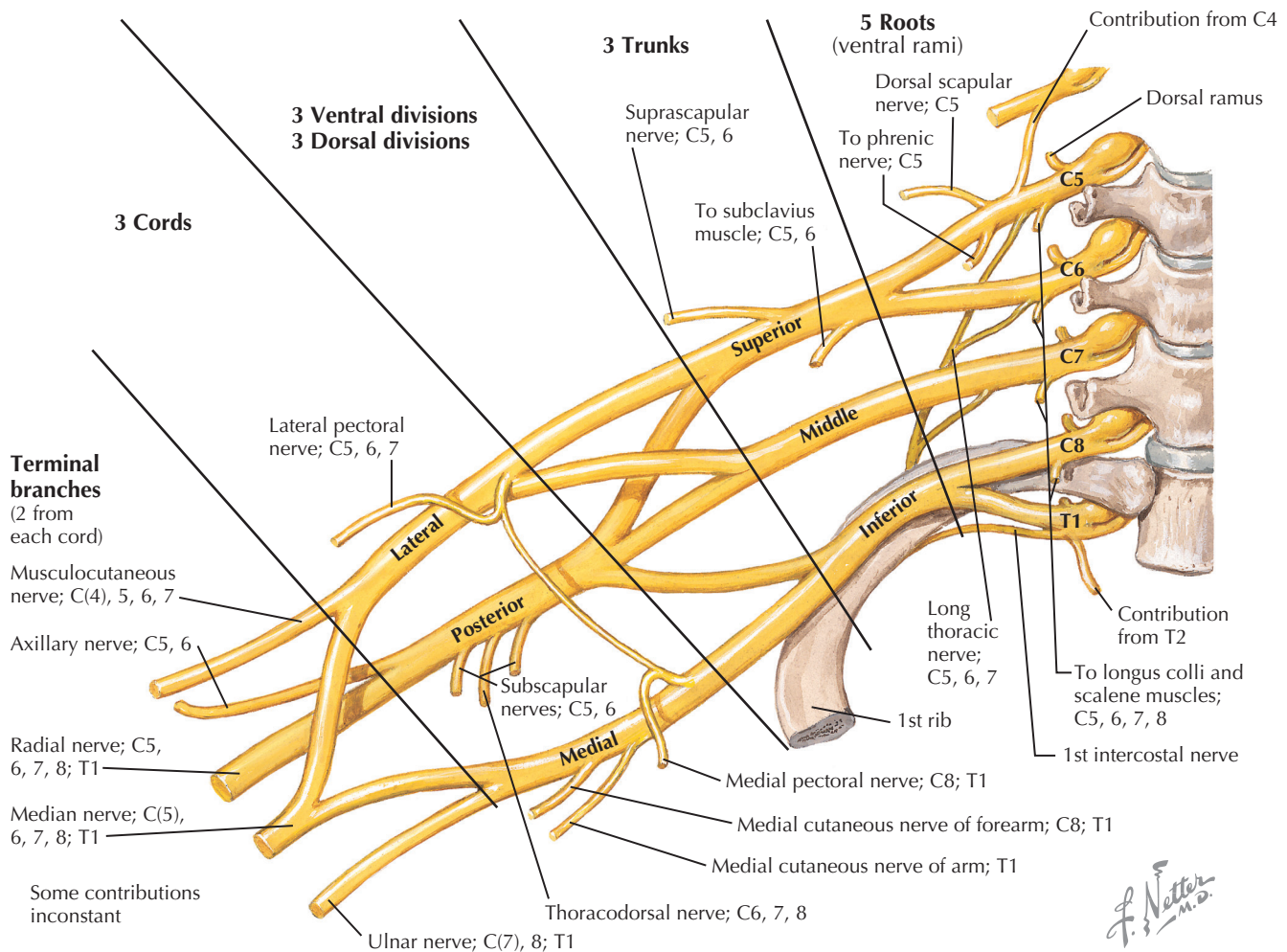


## 9.25 THORACIC NERVES

The 12 pairs of thoracic nerves are derived from dorsal and ventral roots of their corresponding segments. These nerves do not form plexuses; they distribute cutaneous branches to the thoracic dermatomes and send other sensory fibers to deeper muscular structures, vessels, periosteum, parietal pleura, the peritoneum, and breast tissue. The thoracic nerves

also send motor fibers to muscles of the thoracic and abdominal wall and carry preganglionic and postganglionic sympathetic nerve fibers into and out of the sympathetic chain. Muscles of the thoracic and abdominal wall, supplied by these nerves, act as accessory respiratory muscles and may assist in breathing in times of dyspnea or phrenic nerve impairment.





Supraclavicular Branches		Infraclavicular Branches		Infraclavicular Branches	
<i>From plexus roots</i>		<i>From lateral cord</i>		<i>From posterior cord</i>	
To longus colli and scalene muscles	C5, 6, 7, 8	Lateral pectoral	C5, 6, 7	Ulnar	C(7), 8; T1
Dorsal scapular	C5	Musculocutaneous	C(4), 5, 6, 7	Medial root of median	C8; T1
Branch to phrenic	C5	Lateral root of median	C(5), 6, 7	<i>From medial cord</i>	
Long thoracic	C5, 6, 7	Medial pectoral	C8; T1	Upper subscapular	C5, 6, (7)
<i>From superior trunk</i>		Medial cutaneous nerve of arm	T1	Lower subscapular	C5, 6
Suprascapular	C5, 6	Medial cutaneous nerve of forearm	C8; T1	Axillary (circumflex humeral)	C5, 6
To subclavius muscle	C5, 6			Thoracodorsal	C5, 6
				Radial	C5, 6, 7, 8

## 9.26 BRACHIAL PLEXUS

The brachial plexus is formed by the union of the ventral roots of C5 through C8 plus T1, with a smaller contribution from C4. Sensory and sympathetic fibers also distribute in the brachial plexus. The roots give rise to three trunks, three ventral and three dorsal divisions, three cords as well as numerous terminal branches, the peripheral nerves. This plexus is vulnerable to birth injury (superior plexus paralysis), which causes paralysis of the deltoid, biceps, brachial, and brachioradialis muscles, with sparing of the hands, and causes sensory loss over the deltoid area and radial aspect of the forearm and hand. Pressure by a cervical rib can cause inferior plexus injury (C8, T1 injury), which results in paralysis of small hand muscles and flexors of the hand, with ulnar sensory loss and possible Horner's syndrome.

### CLINICAL POINT

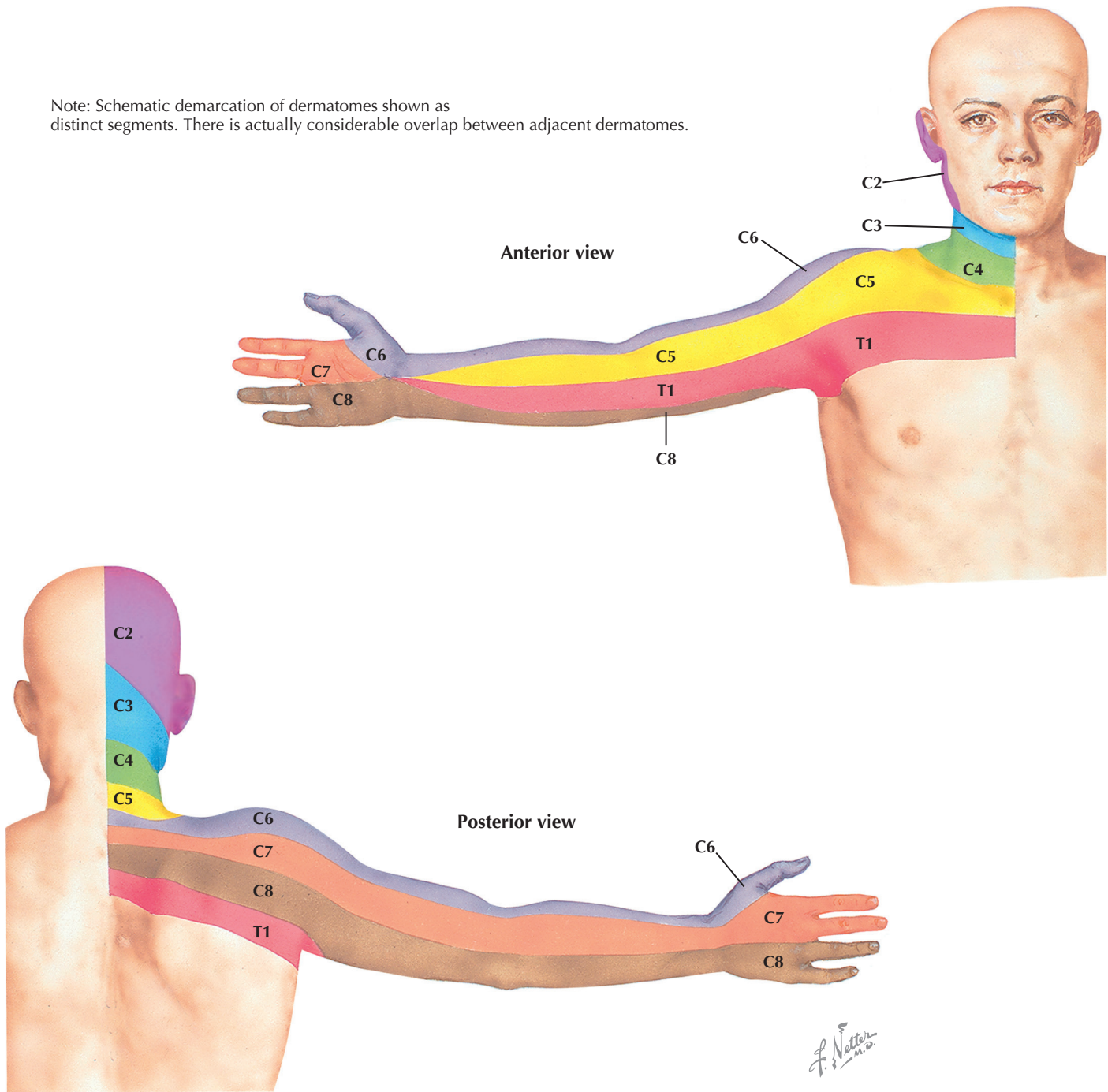
Lesions in the upper brachial plexus, particularly those affecting C5 and C6 contributions, can be caused by traction from a difficult birth,

including displacement of the head to the opposite side and depression of the shoulder on the same side (Erb-Duchenne palsy); by radiation damage, from congenital causes, and by tumors. Such lesions may result in paresis of shoulder abduction and external rotation and in paresis of elbow flexion caused by damage to the motor nerve supply to the deltoid, supraspinatus, infraspinatus, biceps, supinator, and brachioradialis muscles. The arm hangs down and is rotated medially; the forearm is pronated. The biceps and brachioradialis muscle stretch reflexes are absent. Sensory loss is experienced over the deltoid region and along the radial side of the forearm.

Lesions of the lower brachial plexus, particularly those affecting C8 and T1 contributions, can result from traction on an abducted arm, a breech delivery (Dejerine-Klumpke paralysis), an apical lung tumor, a cervical rib, radiation damage, or a tumor. These lesions result in paralysis of finger flexion and paralysis of all the small muscles of the hand; a claw hand results. Sensory loss is present along the ulnar surface of the forearm and hand. Ipsilateral Horner's syndrome is sometimes seen due to damage to T1 preganglionic outflow to the superior cervical ganglion, with resultant ptosis, miosis, and hemianhydrosis.



Note: Schematic demarcation of dermatomes shown as distinct segments. There is actually considerable overlap between adjacent dermatomes.

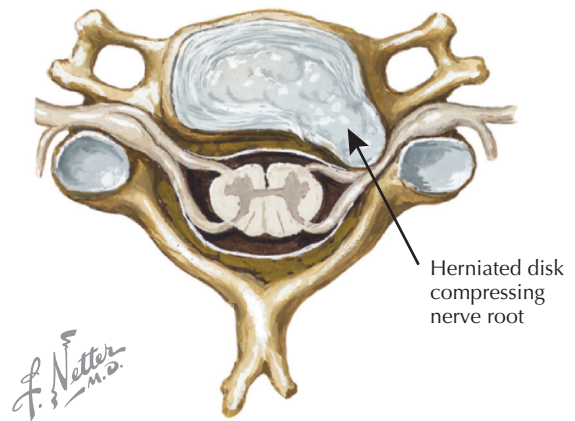
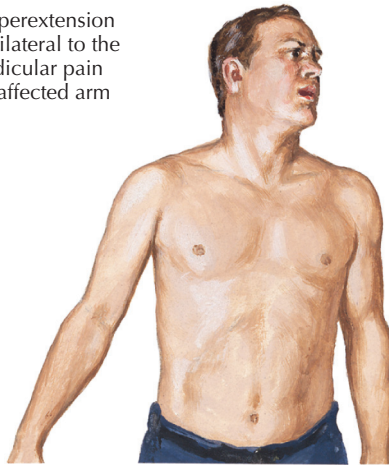


### 9.27 DERMATOMES OF THE UPPER LIMB

Because of the distribution of nerve fibers in the brachial plexus and the interchange of sensory and motor fibers through the trunks, divisions, and cords, the orderly segmental distribution of cervical dermatomes is obscured to some

degree. However, the arrangement of dermatomes in the upper limb is explicable embryologically as limb buds extend. The more proximal dermatomes are elongated strips located along the outer sides of the limbs, whereas the more distal dermatomes are found medially.

Spurling maneuver: hyperextension and flexion of neck ipsilateral to the side of lesion cause radicular pain in neck and down the affected arm

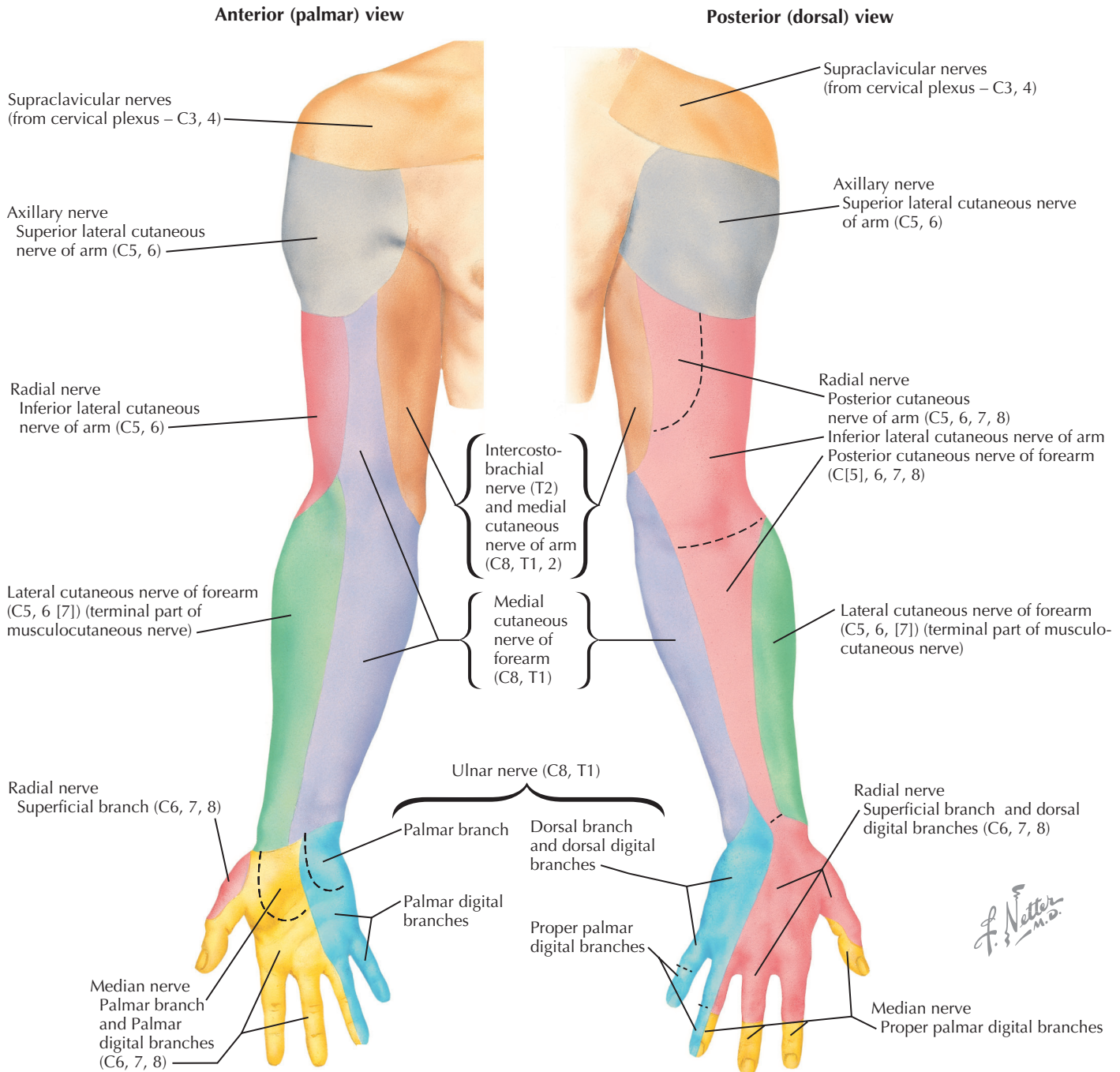


Level	Motor signs (weakness)	Reflex signs	Sensory loss
C5	Deltoid	None	
C6	Biceps brachii	Biceps brachii Weak or absent reflex	
C7	Triceps brachii	Triceps brachii Weak or absent reflex	
C8	Interossei	None	

## 9.28 CERVICAL DISC HERNIATION

Cervical disc herniation is a common neurologic process, often caused by age-related vertebral deterioration and processes other than trauma (a major cause of lumbar disc herniation). The initial manifestation of cervical disc herniation

often is radiating pain (radiculopathy). Cervical nerve roots 5, 6, and 7 emerge above their related vertebral body, while cervical nerve root 8 emerges between vertebrae C7 and T1. This plate illustrates characteristics of cervical disc herniation, including motor, sensory, and reflex manifestations.



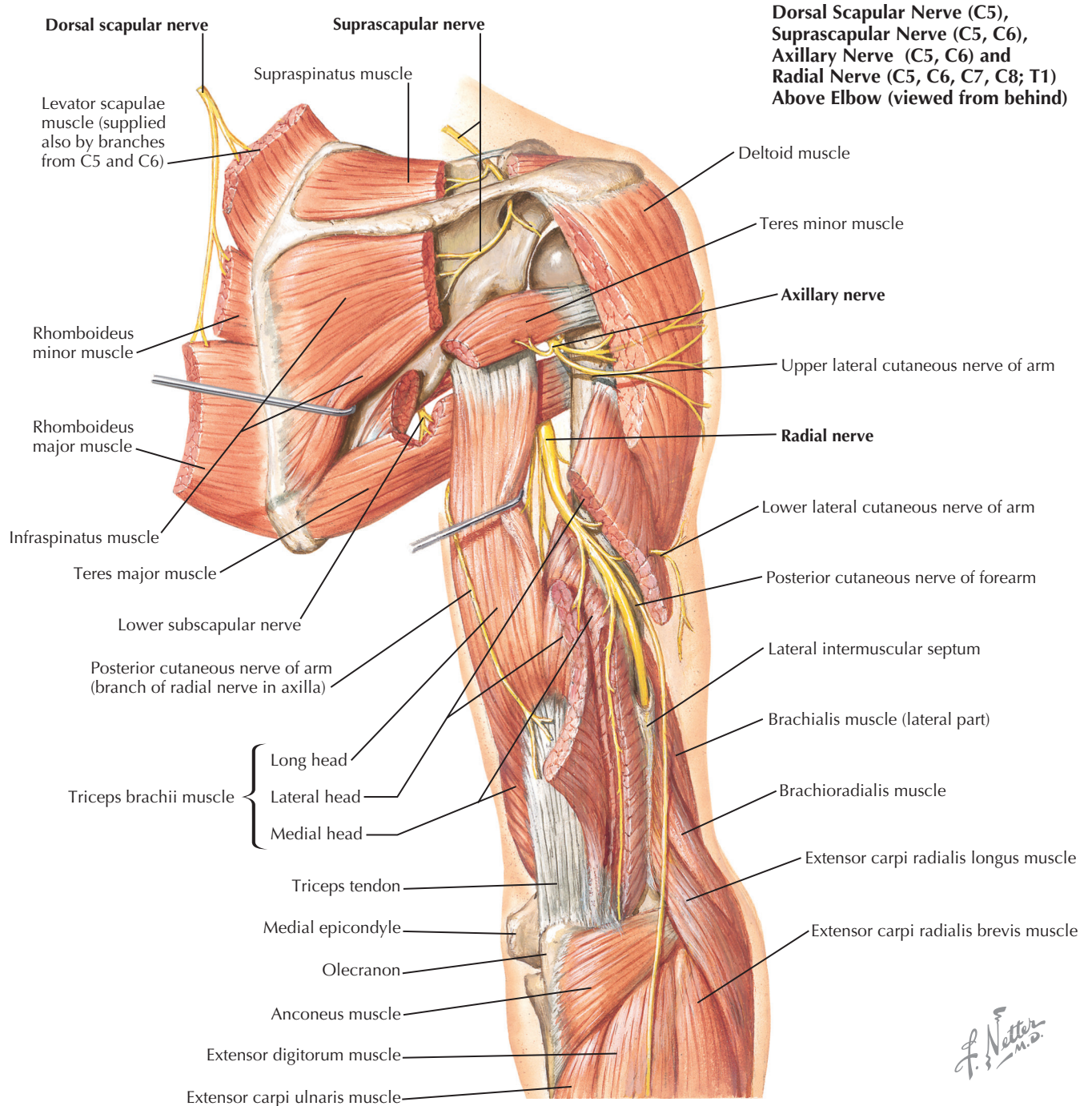
Note: Division is variable between ulnar and radial innervation on dorsum of hand and often aligns with middle of 3rd digit instead of 4th digit as shown.

## 9.29 CUTANEOUS INNERVATION OF THE UPPER LIMB

The cutaneous innervation of the limb derives from the musculocutaneous, axillary, radial, median, and ulnar nerves. These nerves are the terminal branches of the brachial plexus. Unlike the distributions of the dorsal nerve roots, the cutane-

ous sensory distributions of these peripheral nerves to the upper limb do not overlap. Thus, a peripheral nerve injury or compression results in a zone of anesthesia corresponding to its distribution. Irritative lesions result in pain and paresthesias that occur in the same corresponding distribution.



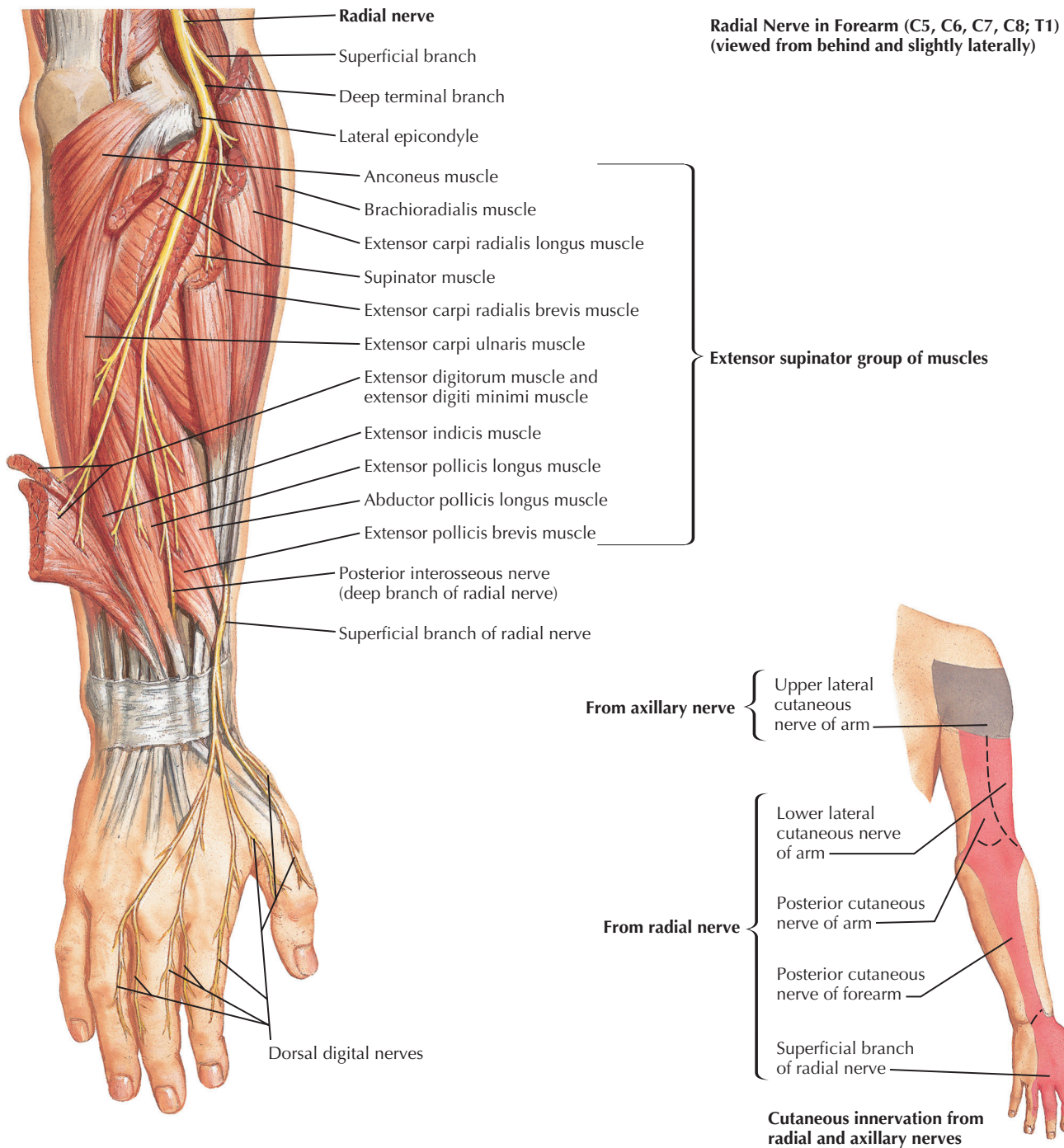


*F. Netter M.D.*

### 9.30 THE SCAPULAR, AXILLARY, AND RADIAL NERVES ABOVE THE ELBOW

The dorsal scapular nerve (C5) supplies the levator scapulae and rhomboid muscles; it aids in elevation and adduction of the scapula toward the spinal column. A nerve lesion leads to lateral displacement of the vertebral border of the scapula and to rhomboid atrophy (difficult to detect). The suprascapular nerve (C5–C6) supplies the supraspinatus and infraspinatus muscles; it aids in lifting and in outward rotation of the arm. A lesion results in weakness in the first 15 degrees of abduction and in external rotation of the arm. The axillary nerve (C5–C6) supplies the deltoid and teres minor muscles; it aids in abduction of the arm to the horizontal and in outward

rotation of the arm. A lesion may be caused by dislocation of the shoulder joint or a fracture of the surgical neck of the humerus and results in deltoid atrophy, in weakness in abduction from 15 degrees to 90 degrees, and in loss of cutaneous sensation over the lower half of the deltoid. The radial nerve (C5–C8) in the upper arm supplies the triceps, anconeus, brachioradialis, extensor carpi radialis, extensor digitorum, and supinator muscles and aids in the extension and flexion of the elbow. A lesion may be caused by a fracture of the midshaft of the humerus that affects the nerve within the spiral groove and leads to paralysis of extension and flexion of the elbow and of supination of the forearm. The wrist and fingers cannot be extended, and wristdrop occurs.

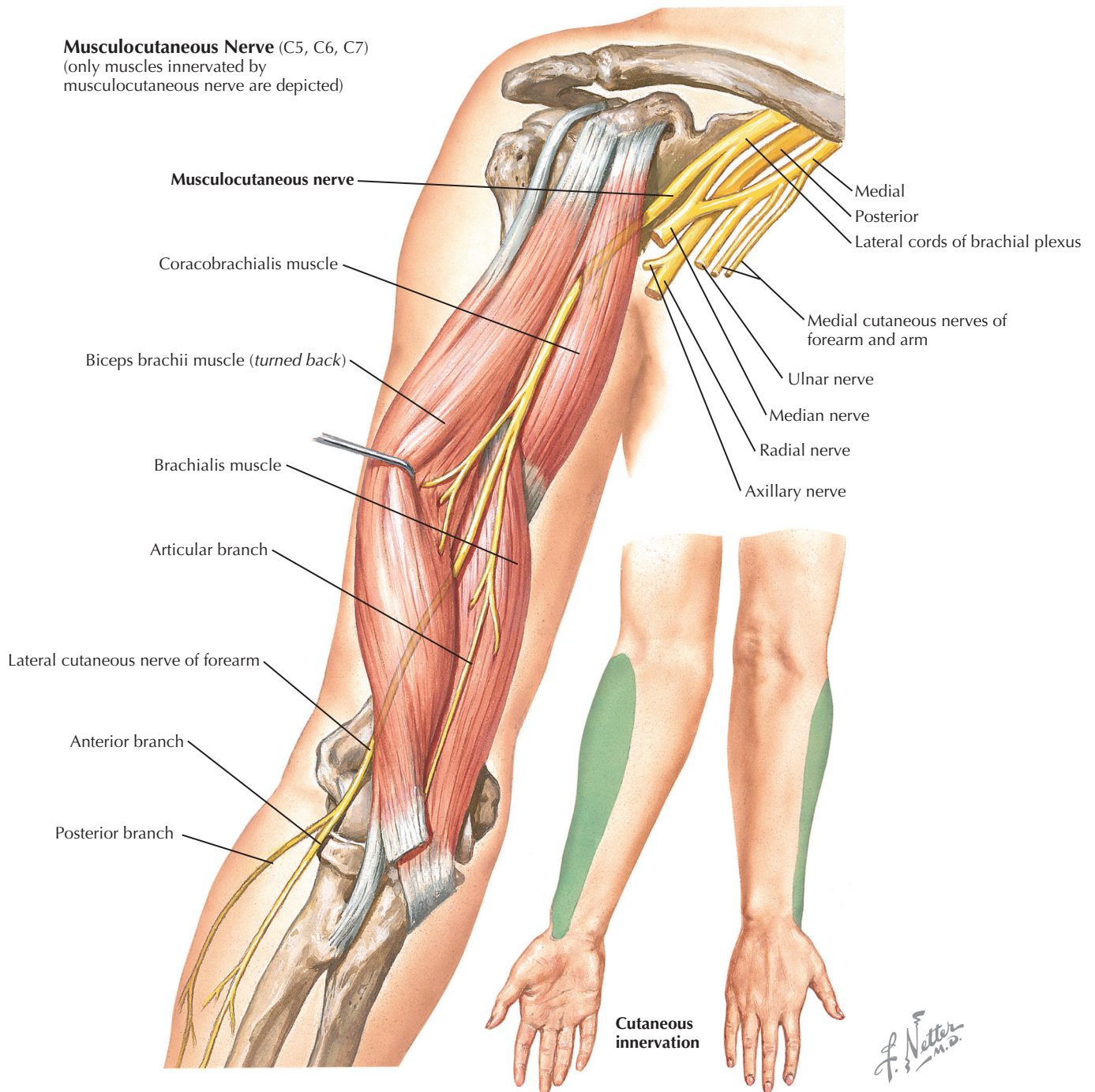


### 9.31 RADIAL NERVE IN THE FOREARM

In the forearm, the radial nerve (C6–C8) supplies motor fibers to the (1) extensor carpi radialis; (2) extensor digitorum; (3) extensor digiti V; (4) extensor carpi ulnaris; (5) supinator; (6) abductor pollicis longus; (7) extensor pollicis brevis and longus; and (8) extensor indicis proprius muscles. It supplies the posterior upper arm, an elongated zone of the posterior

forearm, and the posterior hand, thumb, and lateral  $2\frac{1}{2}$  fingers. A lesion results in paralysis of extension and flexion of the elbow, paralysis of supination of the forearm, paralysis of extension of the wrist and fingers, and paralysis of abduction of the thumb as well as loss of sensation over the radial aspect of the posterior forearm and the dorsum of the hand.





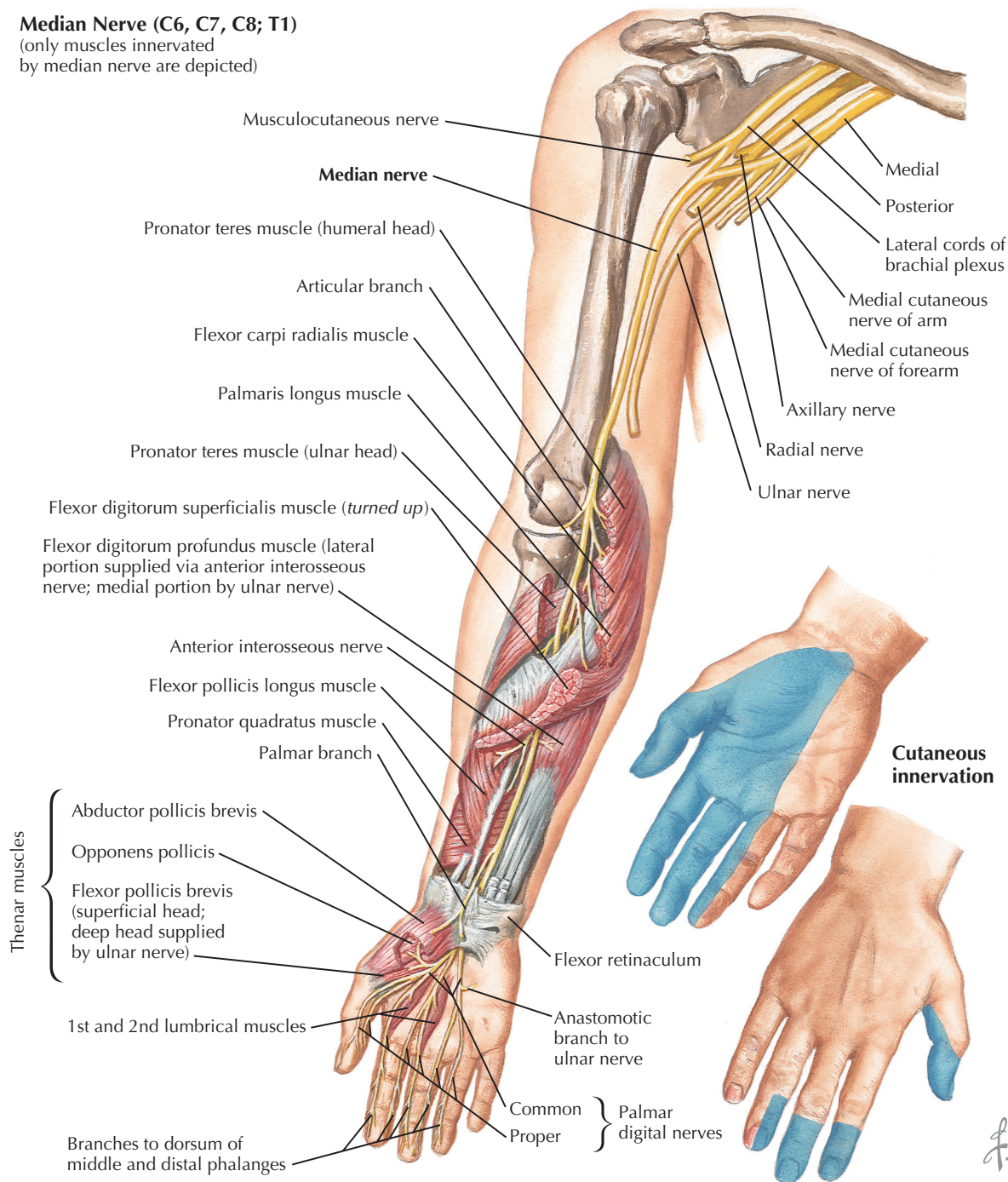
### 9.32 MUSCULOCUTANEOUS NERVE

The musculocutaneous nerve (C5–C6) supplies the biceps brachii, coracobrachialis, and brachialis muscles; it aids in flexion of the upper and lower arm, supination of the lower arm, and elevation and adduction of the arm. The nerve

supplies sensory innervation to the lateral forearm. A lesion may be caused by a fracture of the humerus and results in the wasting of the muscles supplied, weakness of flexion of the supinated arm, and loss of sensation on the lateral forearm.



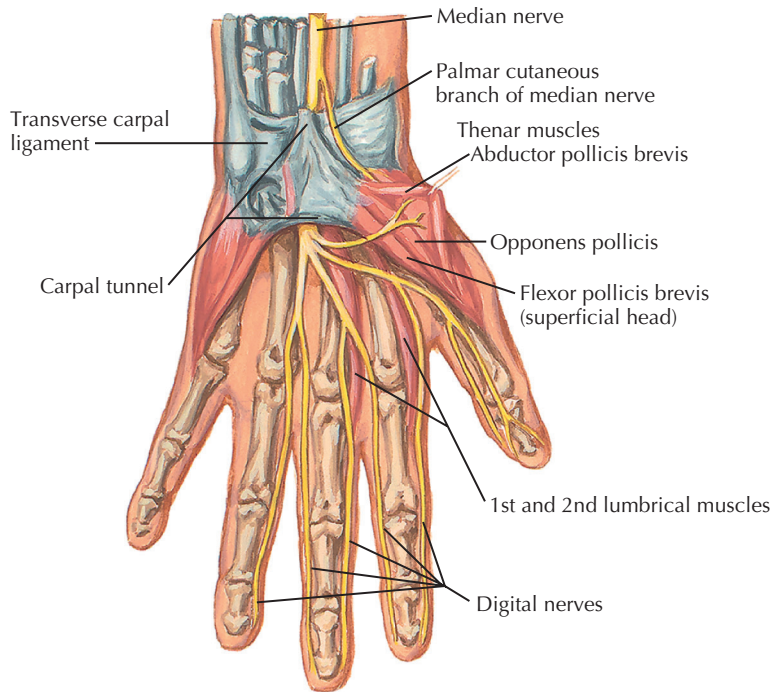
**Median Nerve (C6, C7, C8; T1)**  
(only muscles innervated  
by median nerve are depicted)



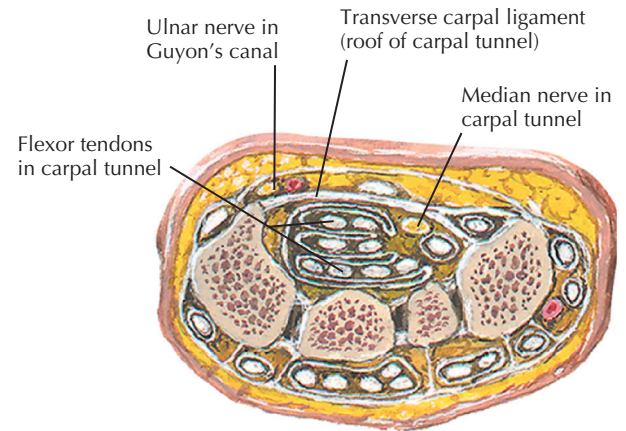
### 9.33 MEDIAN NERVE

The median nerve (C5–T1) supplies motor fibers to the (1) flexor carpi radialis; (2) pronator teres; (3) palmaris longus; (4) flexor digitorum superficialis and profundus; (5) flexor pollicis longus; (6) abductor pollicis brevis; (7) flexor pollicis brevis; (8) opponens pollicis brevis; and (9) lumbrical muscles of the index and middle fingers. It supplies sensory innervation to the palm and adjacent thumb, the index and middle

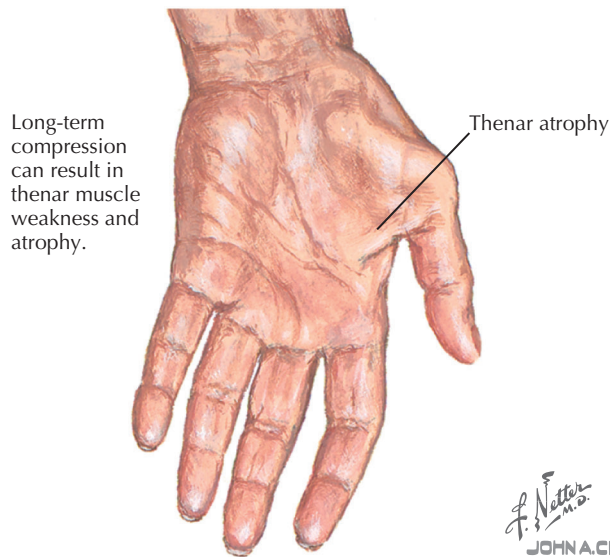
fingers, and the lateral half of the fourth finger. A lesion (caused by carpal tunnel syndrome) results in weakness in flexion of the fingers, abduction and opposition of the thumb, and loss of sensation or painful sensation in the radial distribution in the hand (thumb, index finger, middle finger, and half of the fourth finger). Pain in that distribution often radiates back to the wrist. A higher lesion also produces weakness in pronation of the forearm.



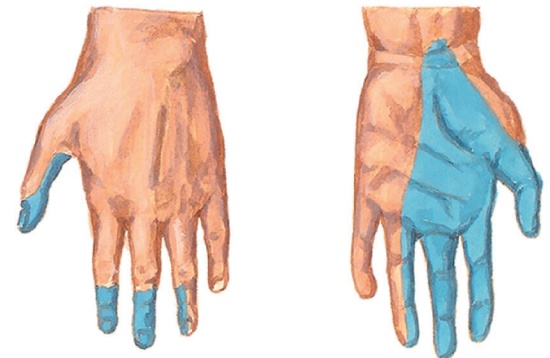
Distribution of branches of median nerve in hand



Activities or medical conditions that increase contents and pressure within tunnel may result in nerve compression.



*F. Netter M.D.*  
JOHN A. CRAIG MD



Sensory distribution of median nerve

### 9.34 CARPAL TUNNEL SYNDROME

The median nerve travels through the carpal tunnel in the wrist. The carpal tunnel is a tightly confined space restricted by the presence of the transverse carpal ligament. Repetitive movements of the wrist (e.g., repeated computer activity), chronic extension of the wrist (e.g., bicycling), and even sleeping with the wrist bent can compress the median nerve in the carpal tunnel. The mechanism of damage to the nerve may be direct compression on the nerve and also may involve an accompanying reduction in blood flow to the nerves through the vasa nervorum. This produces a painful neuropathy char-

acterized by tingling and paresthesias or pain (sometimes severe) on the median side of the palm and in the thumb, the index finger, the middle finger, and the adjacent half of the fourth finger, often radiating back to the wrist. The pain is severe enough to awaken the patient. There also may be weakness in the innervated muscles with atrophy in the thenar eminence. Nerve conduction velocity studies show slowing of motor and sensory axons. An electromyogram may show denervation of innervated muscles such as the abductor pollicis brevis.



**Ulnar Nerve (C8; T1)**  
(only muscles innervated by ulnar nerve are depicted)

**Cutaneous innervation**

Flexor pollicis brevis muscle (deep head only; superficial head and other thenar muscles supplied by median nerve)

Adductor pollicis muscle

**Ulnar nerve** (no branches above elbow)

Articular branch (behind medial condyle)

Flexor digitorum profundus muscle (medial portion only; lateral portion supplied by anterior interosseous branch of median nerve)

Flexor carpi ulnaris muscle (*drawn aside*)

Dorsal branch

Palmar branch

Superficial branch

Deep branch

Palmaris brevis

Abductor digiti minimi

Flexor digiti minimi brevis

Opponens digiti minimi

} Hypothenar muscles

Common palmar digital nerve

Anastomotic branch to median nerve

Palmar and dorsal interossei muscles

3rd and 4th lumbrical muscles (*turned down*)

Proper palmar digital nerves (dorsal digital nerves are from dorsal branch)

Branches to dorsum of middle and distal phalanges

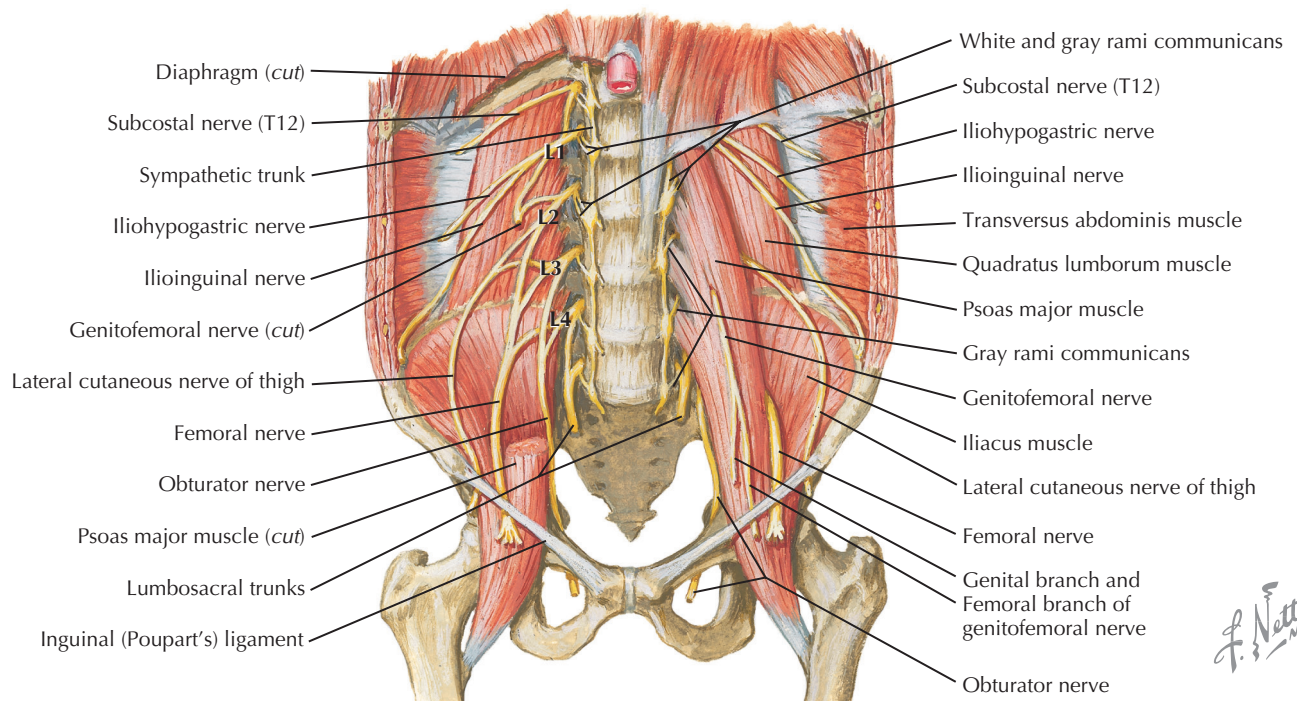
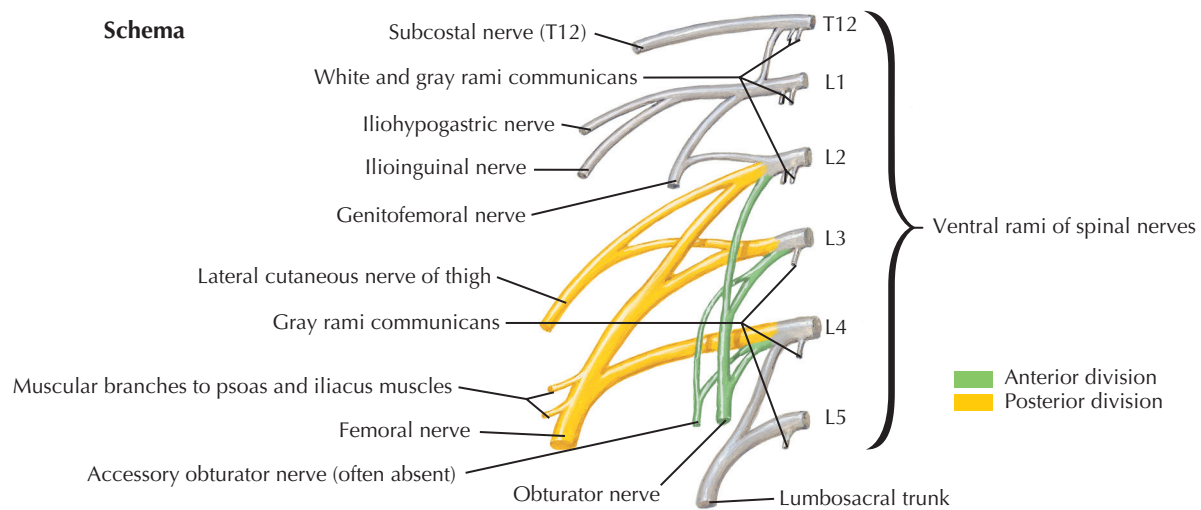
*F. Netter M.D.*

### 9.35 ULNAR NERVE

The ulnar nerve (C8–T1) supplies motor fibers to the (1) flexor carpi ulnaris; (2) flexor digitorum profundus; (3) adductor pollicis; (4) abductor digiti V; (5) opponens digiti V; (6) flexor digiti brevis V; (7) interossei dorsal and palmar; and (8) lumbrical muscles of the fourth and little fingers. It supplies sensory innervation to the dorsal and palmar medial surface of the hand for the little finger and the medial half of

the fourth finger. A lesion results in wasting of hand muscles; weakness of wrist flexion and ulnar deviation of the hand; weakness of abduction and adduction of fingers, known as claw hand (hyperextension of the fingers at metacarpophalangeal joints and flexion at the interphalangeal joints); and loss of sensation in the ulnar distribution in the hand (dorsal and palmar surfaces of the medial hand, the little finger, and the adjacent half of the fourth finger).



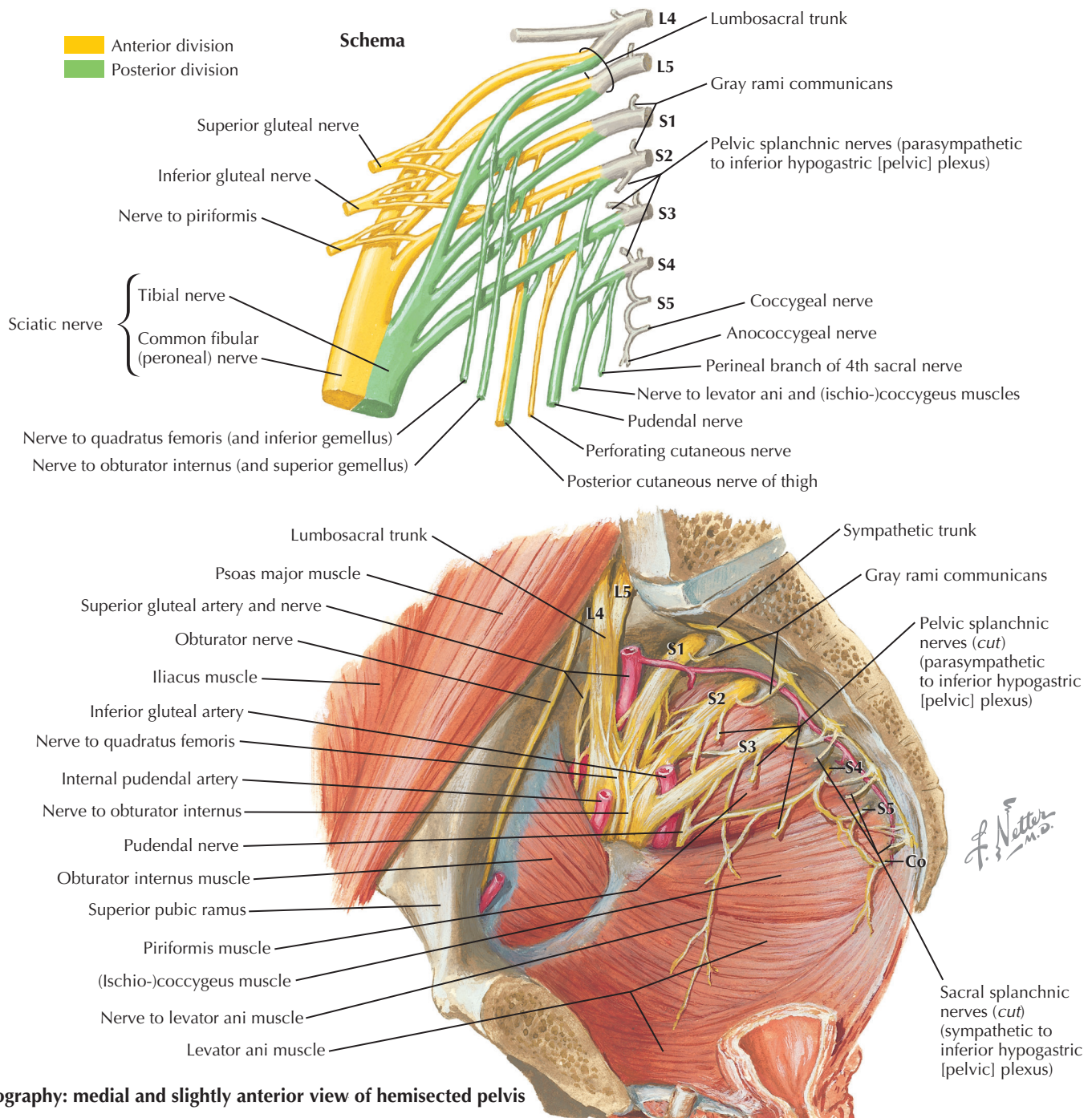


### 9.36 LUMBAR PLEXUS

The lumbar plexus is formed from the anterior primary rami of the L1 through L4 roots within the posterior substance of the psoas muscle. The L1 (and some of L2) root forms the iliohypogastric and ilioinguinal nerves and the genitofemoral nerves. These nerves contribute innervation to the transverse and the oblique abdominal muscles. The remaining roots form the femoral, obturator, and lateral femoral cutaneous nerves. Lesions in the lumbar plexus are unusual because of the protection of the plexus within the psoas muscle. Such lesions result in weakness of hip flexion, weakness of adduction of the thigh and extension of the leg, and decreased sensation on the anterior thigh and leg.

#### CLINICAL POINT

A lumbar plexopathy results in characteristic weakness and sensory losses in nerve roots L2–L4 and involves the distribution of both the obturator and femoral nerves. The most characteristic motor losses are weakness of hip flexion and adduction and weakness of extension of the leg. The motor loss can sometimes occur as the principal finding in a plexopathy but must be distinguished from radiculopathy. Sensory loss over the anterior (and medial) aspect of the thigh may or may not be seen. The patellar reflex usually is diminished. Some lumbar plexopathies present with a patchy motor loss in one or both legs; sometimes the cause is very clear, as in postradiation lumbar plexopathy following treatment of a retroperitoneal tumor or nodes, or in a plexopathy that accompanies pregnancy. And sometimes the cause is not clear, and may include an ischemic diabetic plexopathy, a tumor with infiltration, vasculitis, or trauma. Lumbar plexopathies are usually distinguished from radiculopathies because the latter are painful and are accompanied by a nerve root distribution.



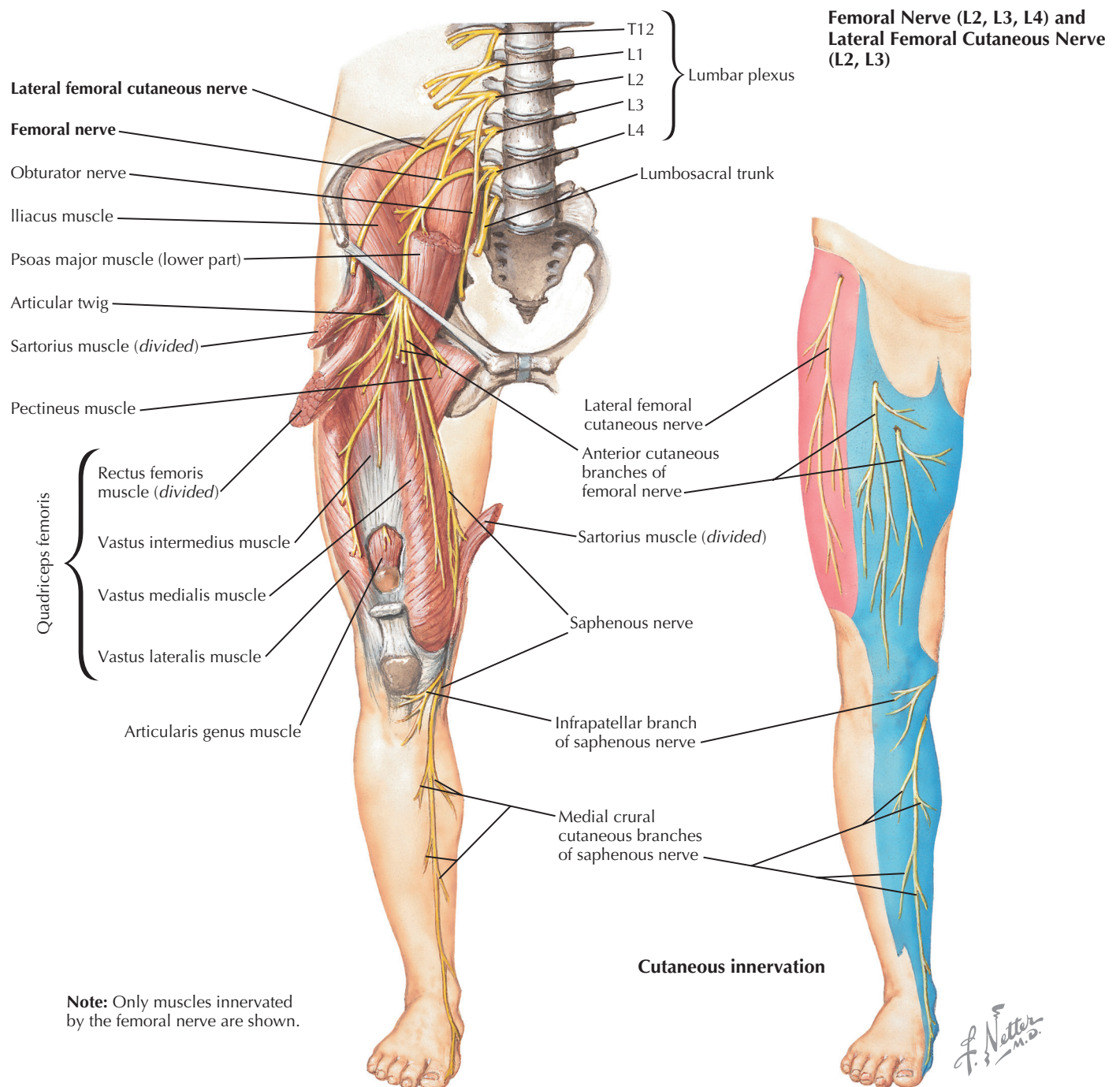
### 9.37 SACRAL AND COCCYGEAL PLEXUSES

The sacral and coccygeal plexuses are formed from the roots of the L4–S4 segments, located anterior to the piriformis muscle. The major branches include the superior (L4–S1) and inferior (L5–S2) gluteal nerves, the posterior femoral cutaneous nerve (S1–S3), the sciatic nerve (L4–S3) and its tibial and common peroneal divisions, and the pudendal nerve (S2–S4). The pudendal nerve supplies the perineal and sphincter muscles, which aid in closing the sphincters of the bladder and the rectum. Lesions of the sacral plexus result in weakness of the posterior thigh and muscles of the leg and feet, with decreased sensation in the posterior thigh and a perianal/saddle location.

#### CLINICAL POINT

Sacral plexopathies usually present as weakness and loss of sensation in the distribution of the gluteal, tibial, and peroneal nerves. The leg weakness can be significant; it includes weakness of hip extension and abduction, weakness of flexion of the leg, and weakness of ankle movements (plantarflexors and dorsiflexors). Weakness may occur in the gluteal muscles if the plexopathy involves more proximal regions of the plexus. Sensory loss can occur in the posterior region of the thigh, the anterolateral and posterior leg, and the plantar surface and dorsolateral portion of the foot. Saddle sensory loss may or may not be present. Some autonomic involvement also may occur, with vascular changes and trophic alterations characteristic of autonomic damage.



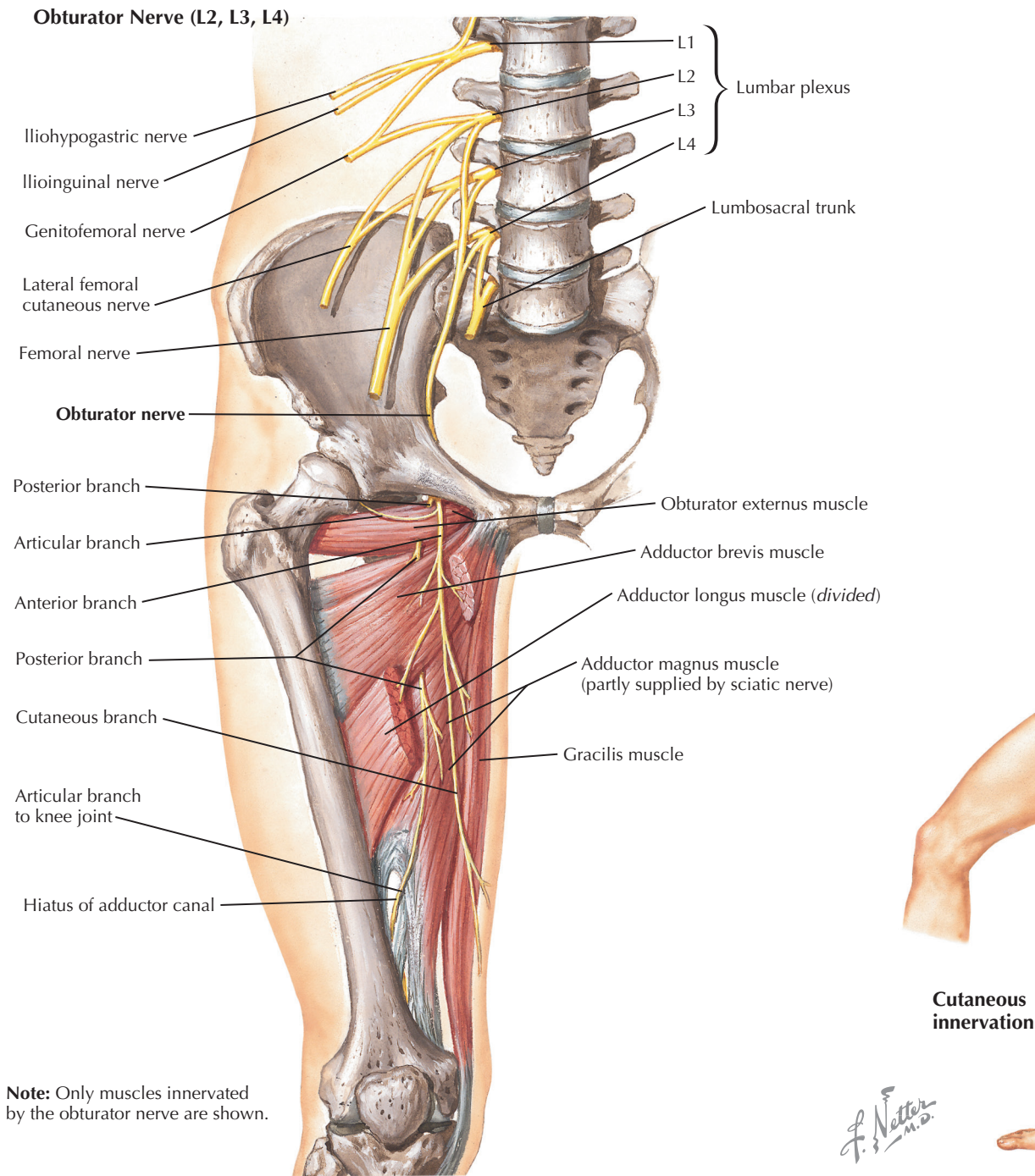


### 9.38 FEMORAL AND LATERAL FEMORAL CUTANEOUS NERVES

The femoral nerve (mainly L2–L4) innervates the iliopsoas, sartorius, and quadriceps femoris muscles. It contributes to flexion and outward rotation of the hip, flexion and inward rotation of the lower leg, and extension of the lower leg around the knee joint. It supplies sensory fibers to the anterior thigh and to the anterior and medial surface of the leg and foot. A lesion results in weakness of extension of the leg and flexion

of the hip and leg, with quadriceps atrophy and in loss of sensation in territories of sensory distribution. The lateral femoral cutaneous nerve supplies sensation to the skin and fascia of the anterior and lateral surfaces of the thigh to the level of the knee. Compression of the nerve at the inguinal ligament or near the surface (caused by a tight-fitting garment) may result in loss of sensation or paresthesias and pain on the anterior and lateral surfaces of the ipsilateral thigh.

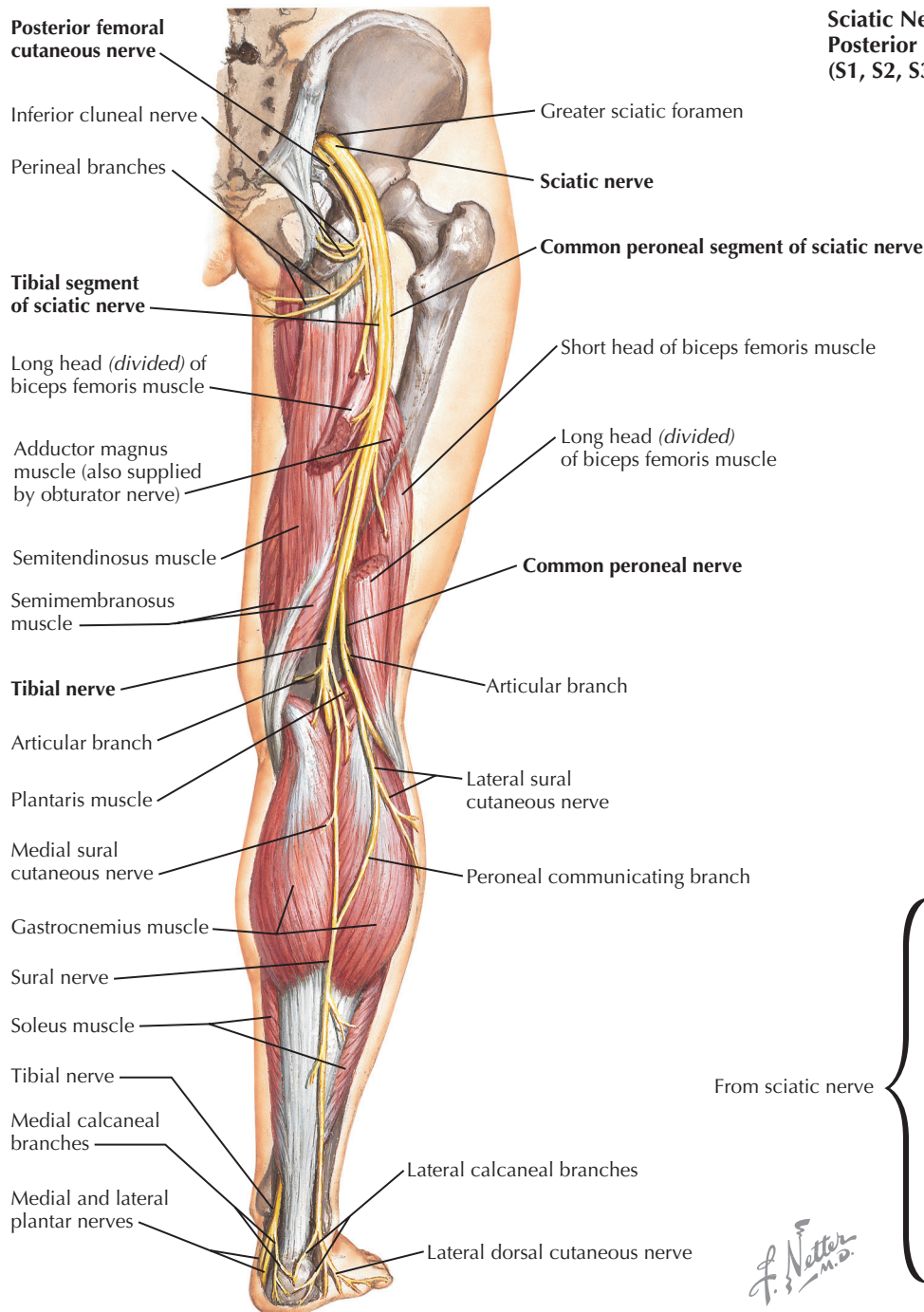




### 9.39 OBTURATOR NERVE

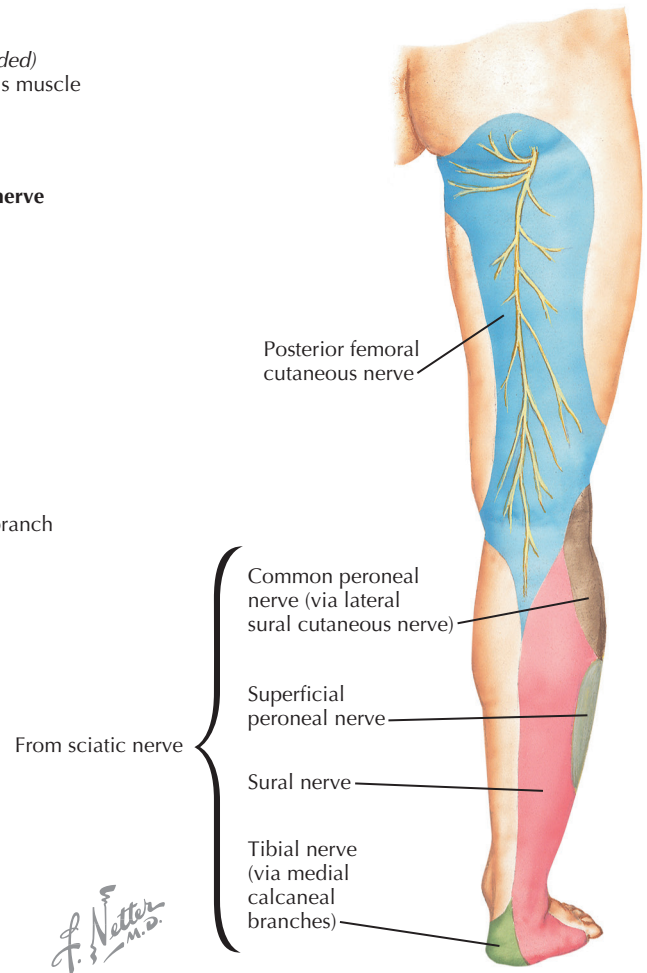
The obturator nerve (L2–L4) supplies the pectineus; adductor (longus, brevis, and magnus); gracilis; and external obturator muscles. This nerve controls adduction and rotation of the thigh. A small cutaneous zone on the internal thigh is supplied

by sensory fibers. A lesion of the obturator nerve results in weakness of adduction of the thigh and a tendency to abduct the thigh in walking. There also is weakness of external rotation of the thigh. A small zone of anesthetic skin on the medial thigh is present.



**Sciatic Nerve (L4, L5; S1, S2, S3) and Posterior Femoral Cutaneous Nerve (S1, S2, S3)**

**Cutaneous innervation**

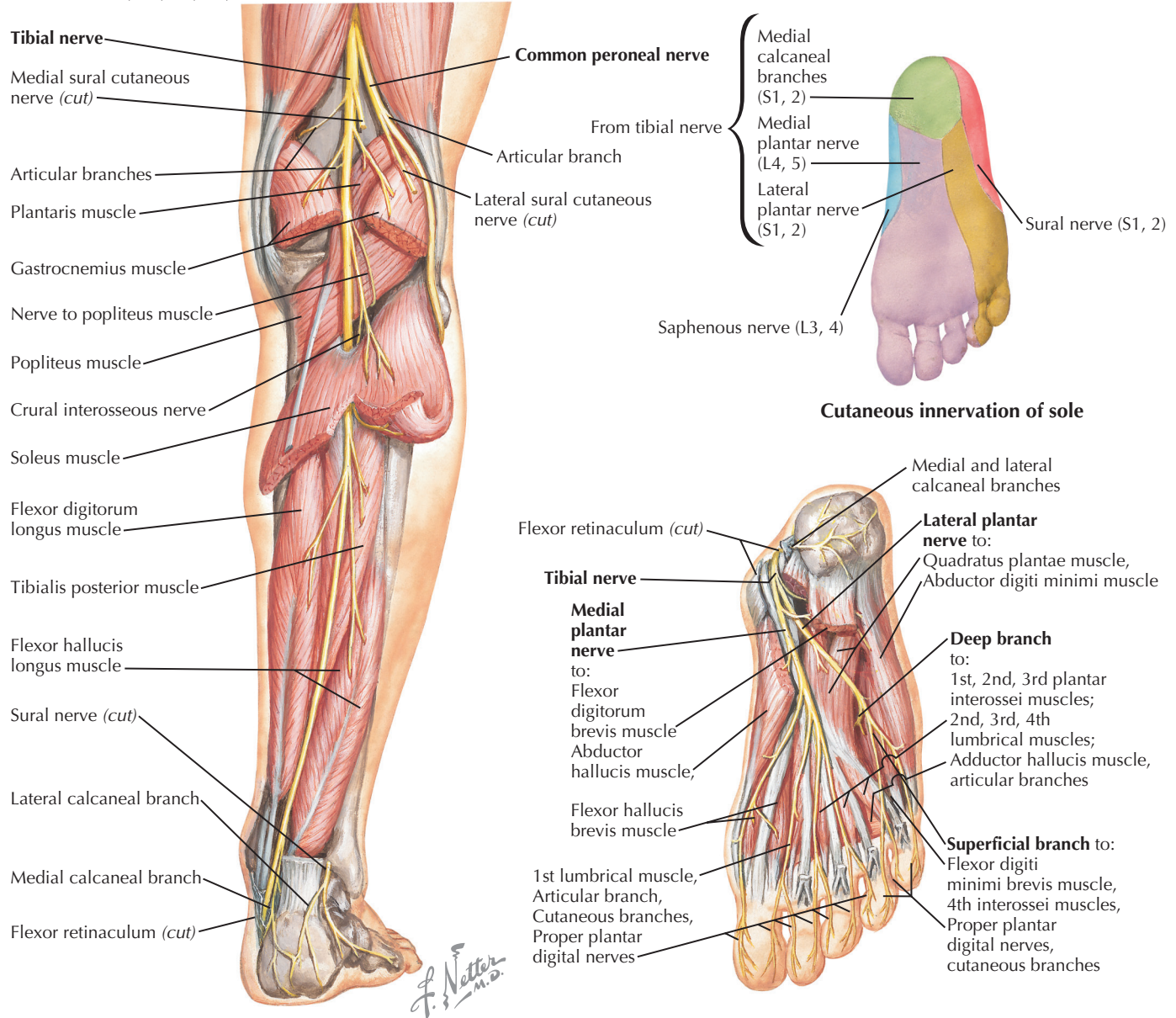


#### 9.40 SCIATIC AND POSTERIOR FEMORAL CUTANEOUS NERVES

The sciatic nerve is formed from the roots of the L4–S3 segments. The superior and inferior gluteal nerves branch proximally, just before the sciatic nerve's formation. The superior gluteal nerve (L4–S1) supplies the gluteus medius and minimus, tensor fascia lata, and piriformis muscles. It contributes to abduction and inward rotation and some outward rotation of the thigh, and to flexion of the upper leg at the hip. The inferior gluteal nerve (L4–S1) supplies the gluteus maximus, obturator internus, gemelli, and quadratus muscles. It contributes to extension of the thigh at the hip and to outward rotation of the thigh. A lesion results in difficulty

climbing stairs and rising from a sitting position. The sciatic nerve proper supplies the biceps femoris, semitendinosus, and semimembranosus muscles (hamstrings) and regulates flexion of the lower leg. Because it branches into the tibial and common peroneal nerves, major lesions of the sciatic nerve result in weakness of leg flexion, weakness of all muscles below the knee, and loss of sensation in the posterior thigh, posterior and lateral aspects of the leg, and sole of the foot. Such lesions may result from a fracture of the pelvis or femur, nerve compression, a herniated disc, or diabetes. The posterior femoral cutaneous nerve (S1–S3) supplies sensory innervation to the posterior thigh, lateral part of the perineum, and lower portion of the buttock.



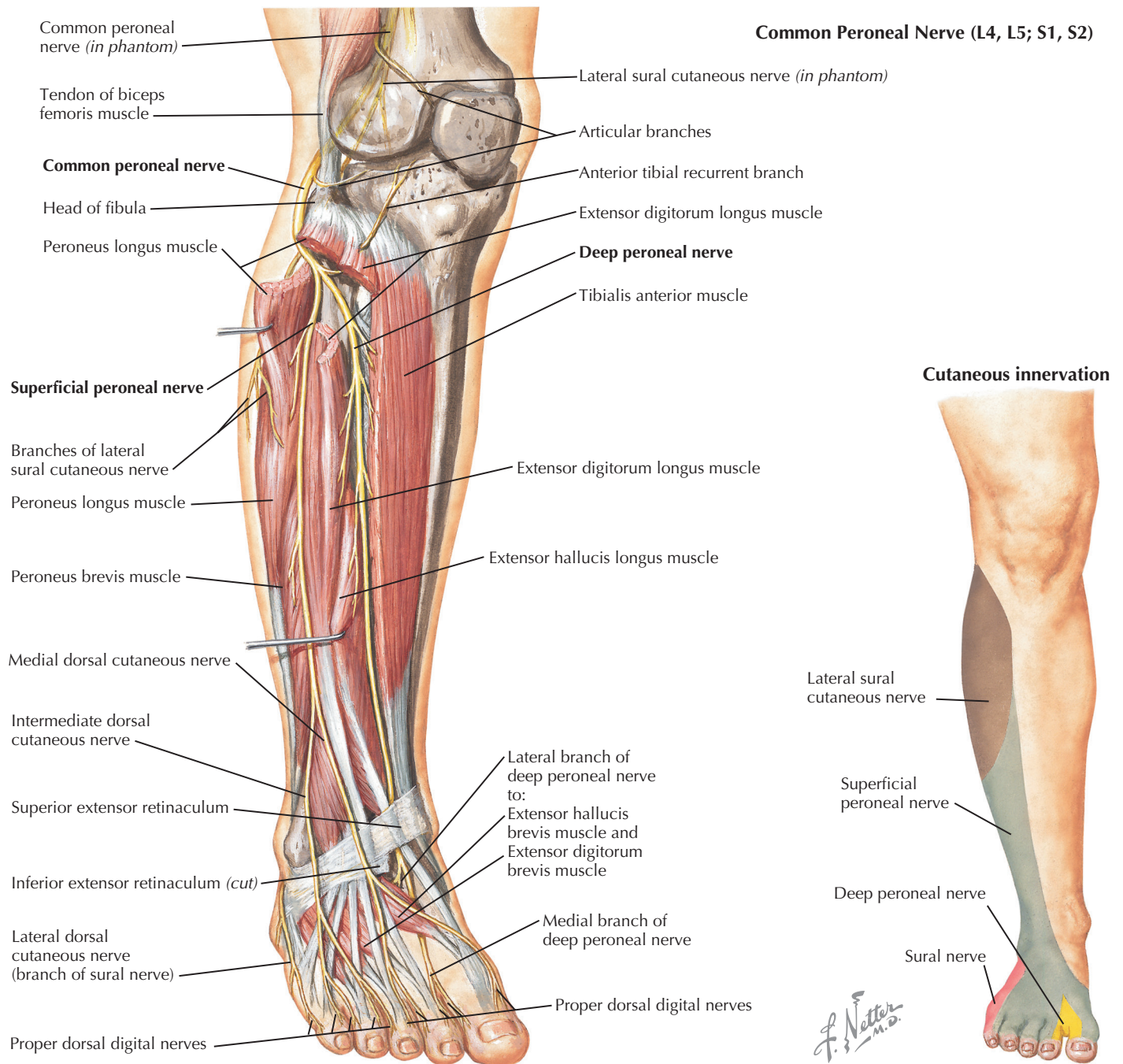
**Tibial Nerve (L4, L5; S1, S2, S3)****9.41 TIBIAL NERVE**

The tibial nerve (L4–S2) supplies innervation to (1) the gastrocnemius and soleus muscles (the main plantar flexors of the foot); (2) the tibialis posterior (plantar flexion and inversion); (3) the flexor digitorum longus (plantar flexor and toe flexor); (4) the flexor hallucis longus (plantar flexor and great toe flexor); and (5) the muscles of the foot, including the abductor digiti minimi pedis, flexor digiti minimi, adductor hallucis, interossei, and third and fourth lumbrical muscles. Sensory branches supply the skin over the lateral calf, foot, heel, and small toe (sural nerve) and the medial aspect of the heel and the sole of the foot (tibial nerve). A lesion can occur because of compression in the tarsal tunnel, a tumor, or diabetes; it results in weakness of plantar flexion and inversion of the foot, weakness of toe flexion, and loss of sensation in the lateral calf and the plantar region of the foot.

**CLINICAL POINT**

The tibial nerve in the popliteal fossa can be used for evaluation of conduction velocity and of specific reflexes. This nerve may be directly stimulated by electrical current. Surface recording electrodes are placed over a distal innervated muscle, and the nerve is stimulated in one or more places, resulting in an indirect evaluation of motor conduction velocity and the muscle response to tibial nerve stimulation. Sensory conduction velocity evaluation is a bit more straightforward; the stimulating electrode is placed at a distal site, and compound action potentials are recorded over at least two proximal sites. A more complex evaluation of reflexes involves evaluation of the muscle stretch (monosynaptic) reflex. With recording electrodes placed over the distal muscle (triceps surae), the tibial nerve is gradually stimulated first by weak and then by stronger electrical current in the popliteal fossa. The first axons that are stimulated are the Ia afferents, which conduct action potentials into the spinal cord and excite the homonymous LMN, whose axon then sends action potentials down to the innervated muscle. This is a long-latency response, called the H wave or H reflex because it involves both the sensory and the motor arms of the muscle stretch reflex. As current strength is increased, the LMN axon is finally stimulated directly, and the muscle response (direct muscle activation) occurs and with a far shorter latency. This H reflex evaluation is useful in assessment of axonal neuropathies and demyelinating neuropathies.

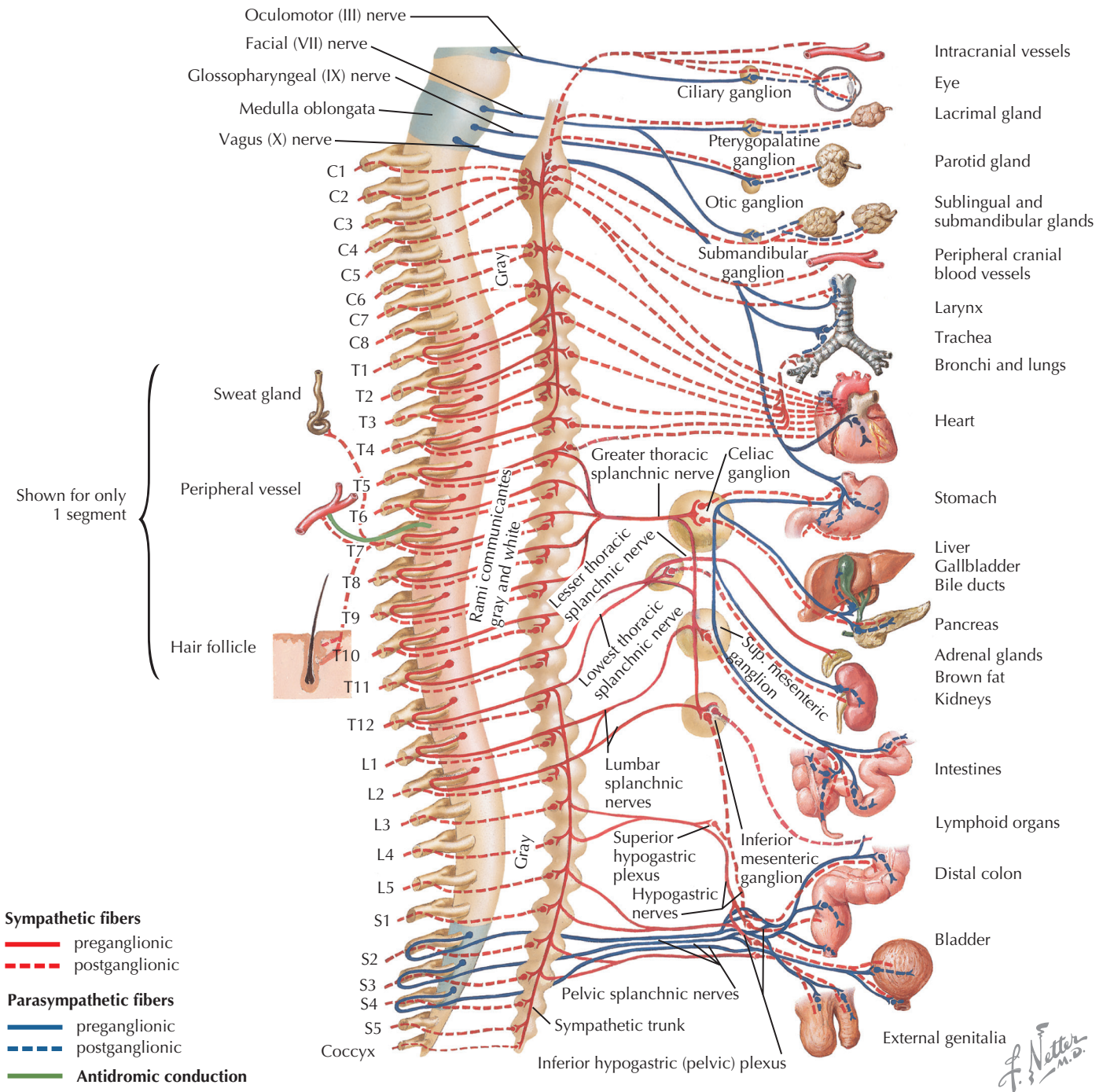




### 9.42 COMMON PERONEAL NERVE

The common peroneal nerve (L4–S1) branches into the deep peroneal nerve, supplying (1) the tibialis anterior (foot dorsiflexion and inversion); (2) the extensor hallucis longus (foot dorsiflexion and great toe extension); (3) the extensor digitorum longus (extension of the toes and foot dorsiflexion); and (4) the extensor digitorum brevis muscles (extension of toes) and the superficial peroneal nerve, which supplies the peroneus longus and brevis muscles (plantar flexion and foot eversion).

Sensory branches supply the lateral aspect of the leg below the knee and the skin on the dorsal surface of the foot. This nerve may be damaged by compression, a fracture at the head of the fibula, or diabetes, resulting in weakness of dorsiflexion and eversion of the foot, weakness of toe extension (dorsiflexion), and loss of sensation in the lateral aspect of the lower leg and the dorsum of the foot.



## AUTONOMIC NERVOUS SYSTEM

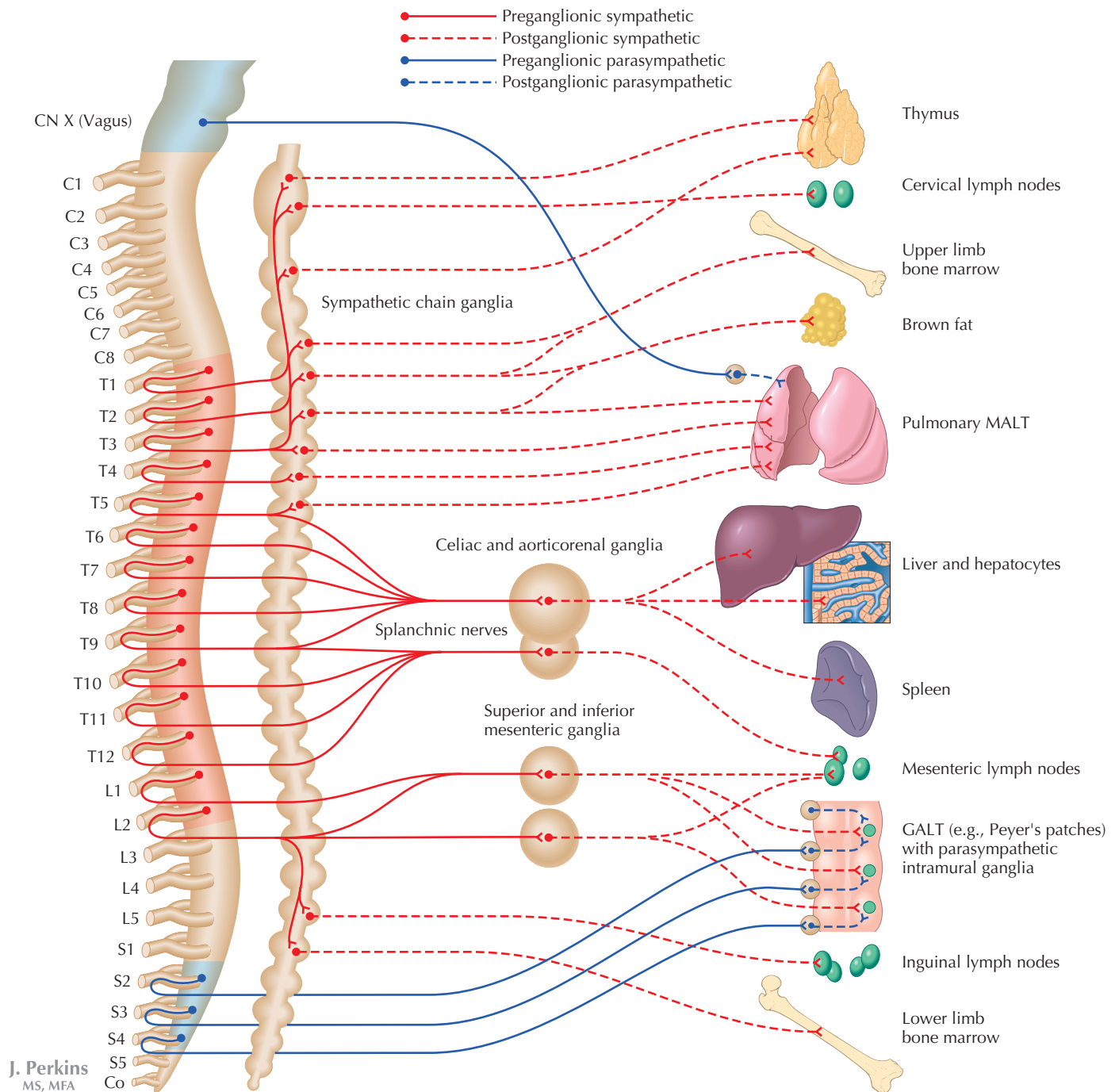
### 9.43 GENERAL SCHEMA

The autonomic nervous system is a two-neuron chain. The preganglionic neuron arises from the brain stem or spinal cord and synapses on postganglionic neurons in the sympathetic chain or collateral ganglia (sympathetic) or on intramural ganglia (parasympathetic) near the organ innervated. The sympathetic division, derived from neurons in the T1–L2 lateral horn, prepares the body for fight-or-flight mobilization for emergency responses. The parasympathetic division, derived from neurons in the brain stem (CNs III, VII, IX, and X) and the sacral spinal cord (S2–S4 intermediate gray) regulates reparative, homeostatic, and digestive functions. These autonomic systems achieve their actions through innervation

of smooth muscle, cardiac muscle, secretory (exocrine) glands, metabolic cells (hepatocytes, fat cells), and cells of the immune system. Normally, both autonomic divisions work together to regulate visceral activities such as respiration, cardiovascular function, digestion, and some endocrine functions.

#### CLINICAL POINT

Pure autonomic failure is a gradual deterioration of sympathetic postganglionic neurons; it occurs in middle-aged individuals and is observed more commonly in men than in women. This syndrome includes neurogenic orthostatic hypotension (syncope or dizziness when standing), inability to sweat, urinary tract dysfunction, erectile dysfunction, and retrograde ejaculation. Pure autonomic failure can be present without evidence of involvement of the CNS. Catecholamine challenge results in robust reactivity in target organs caused by denervation hypersensitivity.

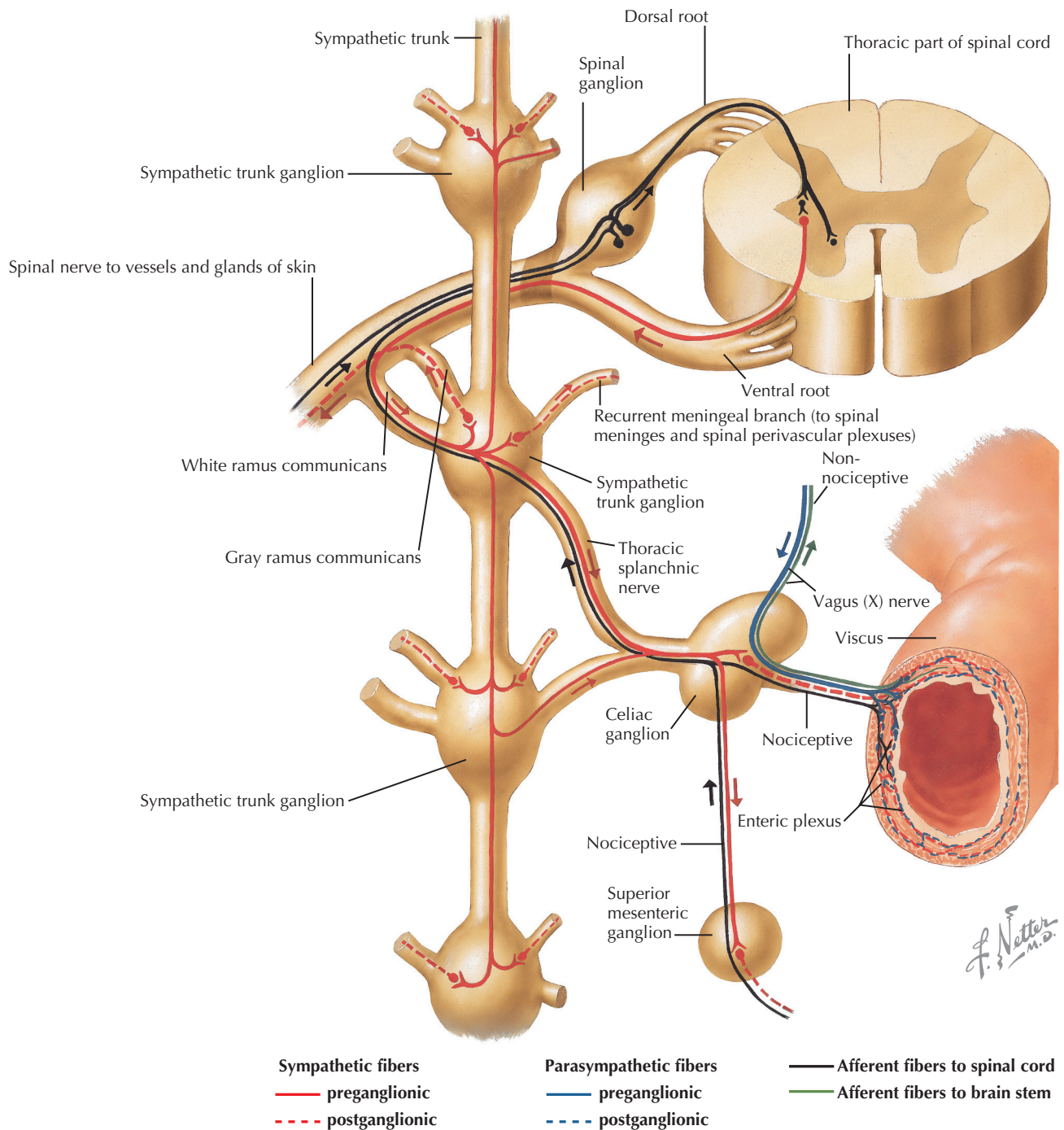


#### 9.44 AUTONOMIC INNERVATION OF THE IMMUNE SYSTEM AND METABOLIC ORGANS

The autonomic nervous system innervates the vasculature, smooth muscle tissue, and parenchyma of organs of the immune system mainly through the sympathetic division. In the bone marrow and thymus, sympathetic fibers modulate cell proliferation, differentiation, and mobilization. In the spleen and lymph nodes, sympathetic fibers modulate innate immune reactivity, and the magnitude and timing of acquired immune responses, particularly the choice of cell-mediated (Th1 cytokines) as opposed to humoral (Th2 cytokines) immunity. Autonomic nerve fibers regulate immune responses

and inflammatory responses in the mucosa-associated lymphoid tissue (MALT) in the lungs, the gut-associated lymphoid tissue (GALT), and the skin. Extensive neuropeptidergic innervation, derived from both the autonomic nervous system and the primary sensory neurons, also is present in the parenchyma of lymphoid organs. Many subsets of lymphoid cells express cognate receptors for catecholamines (alpha and beta receptor subsets) and neuropeptides; the expression of these neurotransmitter receptors is highly regulated by both lymphoid and neural molecular signals. Postganglionic sympathetic nerve fibers also directly innervate hepatocytes and fat cells. (Th = T helper cells)



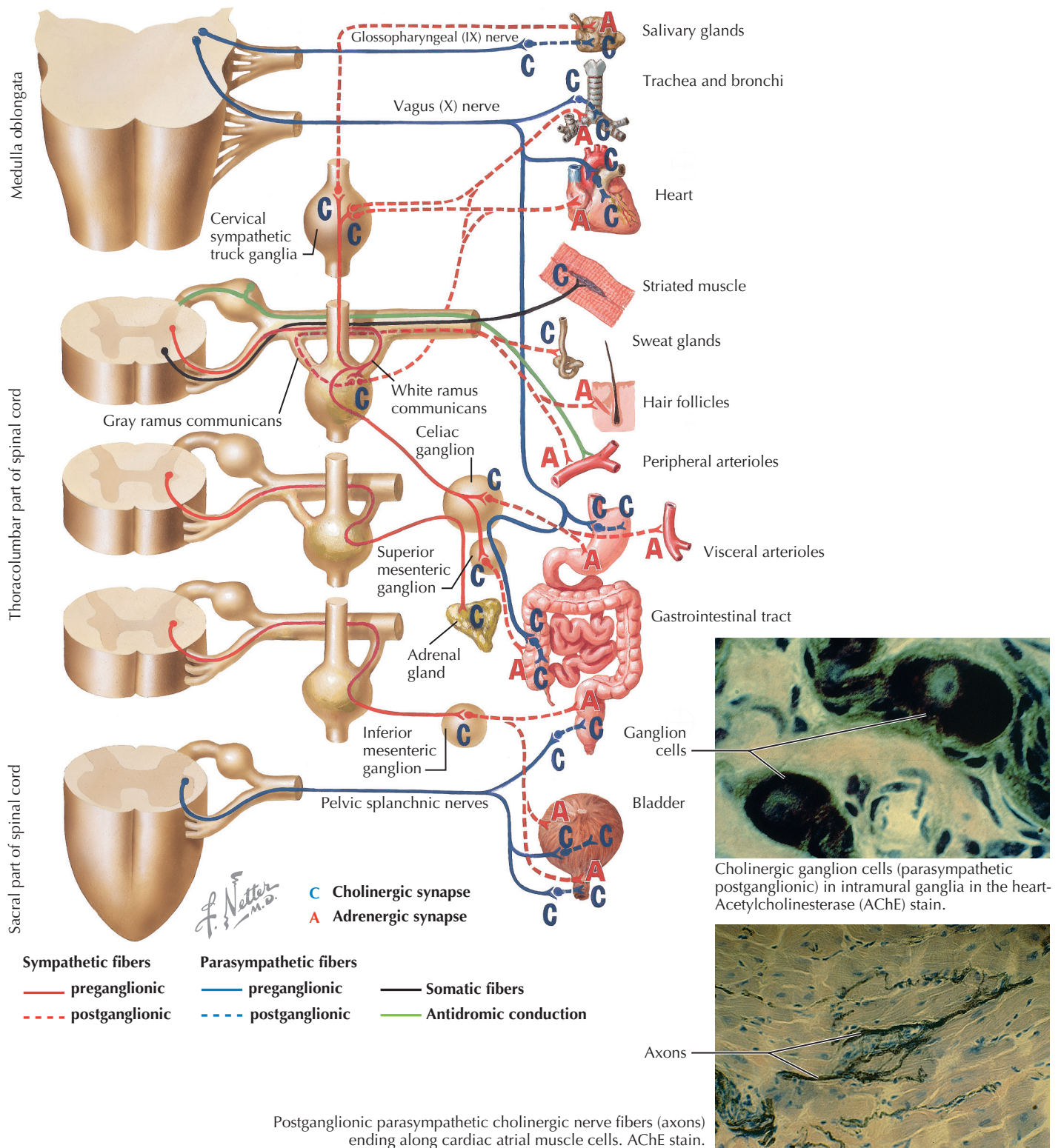


### 9.45 REFLEX PATHWAYS

Autonomic reflex pathways consist of a sensory (afferent) component, interneurons in the CNS, and autonomic efferent components that innervate the peripheral tissue responding to the afferent stimulus. The afferents can be either autonomic (e.g., from the vagus nerve) and processed by brain stem nuclei such as the nucleus solitarius; or they can be somatic (e.g., nociception) and processed by spinal cord neurons. The preganglionic sympathetic or parasympathetic neurons are activated through interneurons to produce a reflex autonomic response (e.g., contraction of vascular smooth muscle to alter blood pressure and increase heart rate and contractility). The efferent connectivity can be relayed via splanchnic or somatic nerves because of the complexity of autonomic efferent pathways.

#### CLINICAL POINT

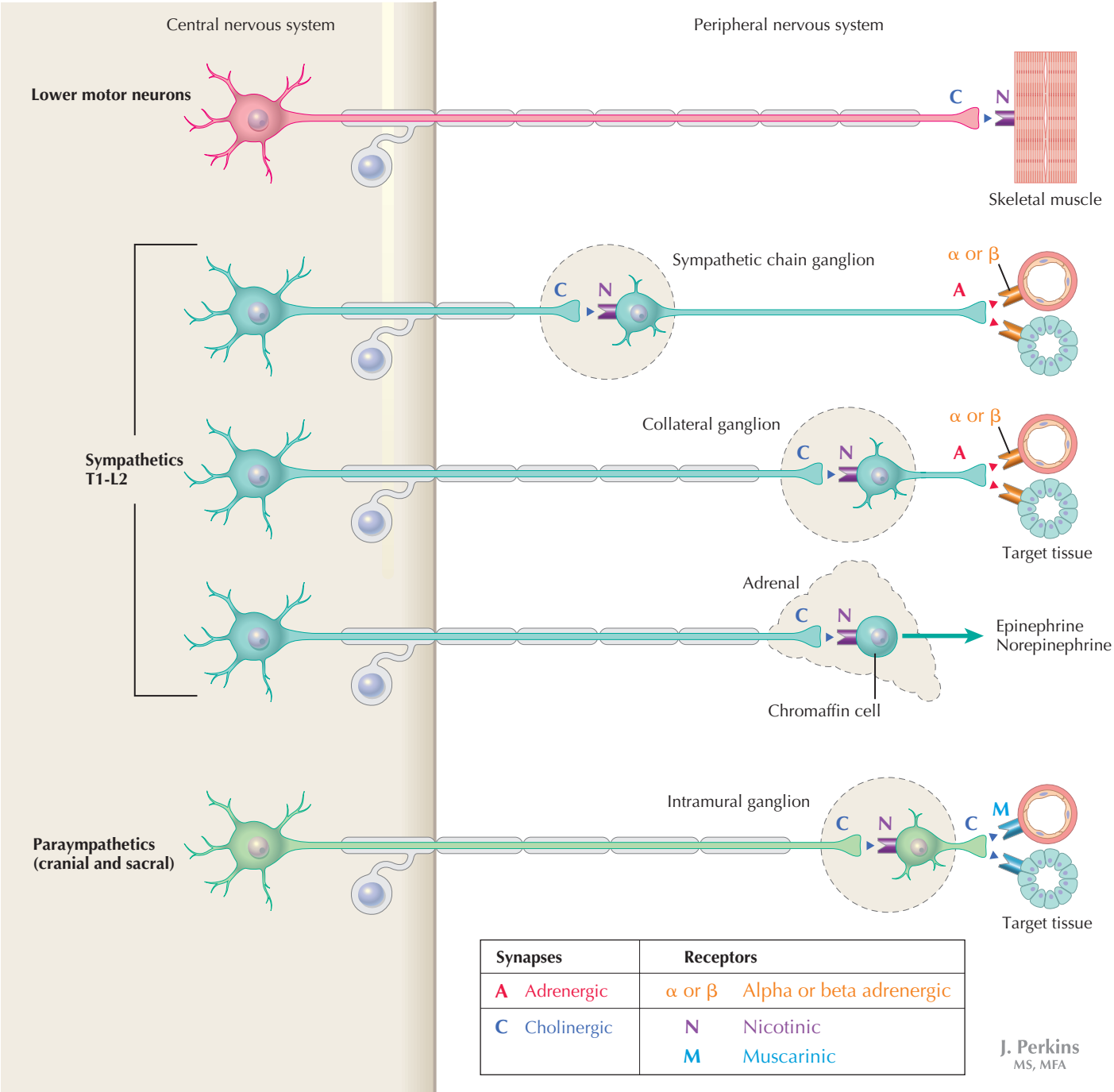
Autonomic reflex pathways are vital for maintenance of homeostasis. Sensory signals associated with standing result in vascular constriction induced by sympathetic neurons to maintain blood pressure, prevent pooling of blood in the lower extremities, and maintain appropriate perfusion of the brain and other vital organs. Nociceptive stimulation may result in reflex elevation of heart rate, blood pressure, and other characteristics of sympathetic activation. Stimulation of the perioral region, particularly in an infant during feeding, activates a parasympathetic state to enhance digestion and diminish sympathetic activation, thereby promoting growth and development. Problems can arise when autonomic reflexes are disrupted, or when hyperactivation of reflex pathways elevates either parasympathetic or sympathetic activity. In such circumstances, there is often a counterpart activation of the other system, as when paradoxical parasympathetic activation leads to compensatory sympathetic activation. This can increase the likelihood of problems such as arrhythmia or even cardiac arrest.



### 9.46 CHOLINERGIC AND ADRENERGIC SYNAPSES

The autonomic nervous system is a two-neuron chain. All preganglionic neurons, sympathetic and parasympathetic, use ACh as the principal neurotransmitter in synapses on ganglion cells. These cholinergic (C) synapses activate mainly nicotinic receptors on the ganglion cells. Postganglionic parasympathetic neurons use ACh at synapses with target tissue,

activating mainly muscarinic receptors. Postganglionic sympathetic neurons use mainly norepinephrine (adrenergic responses; A), to activate both alpha and beta receptors on target tissues. Although ACh and norepinephrine are the principal neurotransmitters used by autonomic neurons, many colocalized neuropeptides and other neuromediators are also present, including neuropeptide Y, substance P, somatostatin, enkephalins, histamine, glutamate, and others.

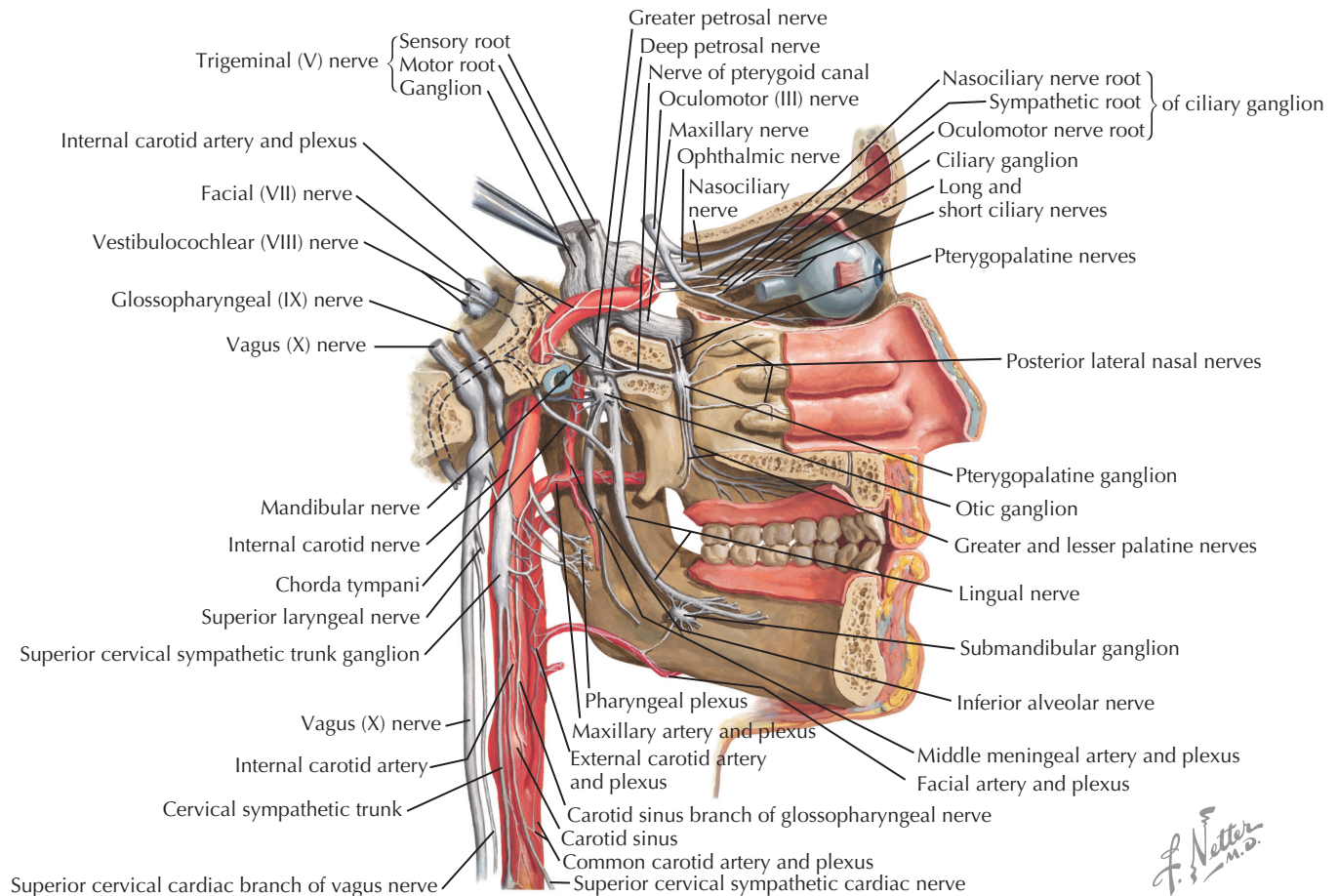


9.47 SCHEMATIC OF CHOLINERGIC AND ADRENERGIC DISTRIBUTION TO MOTOR AND AUTONOMIC STRUCTURES

All preganglionic neurons of both the SNS and the PsNS use ACh as their neurotransmitter. All ganglion cells possess mainly nicotinic receptors for fast response to cholinergic release from preganglionic axons. However, additional muscarinic receptors and dopamine receptors on ganglion cells help to mediate longer term excitability. The postganglionic

sympathetic nerves use mainly norepinephrine as their neurotransmitter, and target structures in the periphery possessing different subsets of alpha and beta adrenergic receptors for response to norepinephrine. Some postganglionic nerve fibers to sweat glands use ACh as their neurotransmitter. Postganglionic parasympathetic nerves use ACh as their neurotransmitter, and target structures in the periphery possessing mainly muscarinic receptors for response to ACh.





#### 9.48 AUTONOMIC DISTRIBUTION TO THE HEAD AND NECK: MEDIAL VIEW

Autonomic nerve distribution to the head and neck includes components of both the SNS and the PsNS. The parasympathetic components are associated with CNs III (ciliary ganglion); VII (pterygopalatine, submandibular ganglia); and IX (otic ganglion). The vagus nerve and its associated ganglia do not innervate effector tissue in the head and neck, although they are present in the neck. Sympathetic components are associated with the superior cervical ganglion and, to a lesser extent, the middle cervical ganglion. The geniculate ganglion (CN VII); petrosal ganglion (CN IX); and nodose ganglion (CN X) process taste information. They are sometimes thought of as autonomic afferents, but they are not components of the autonomic efferent nervous system.

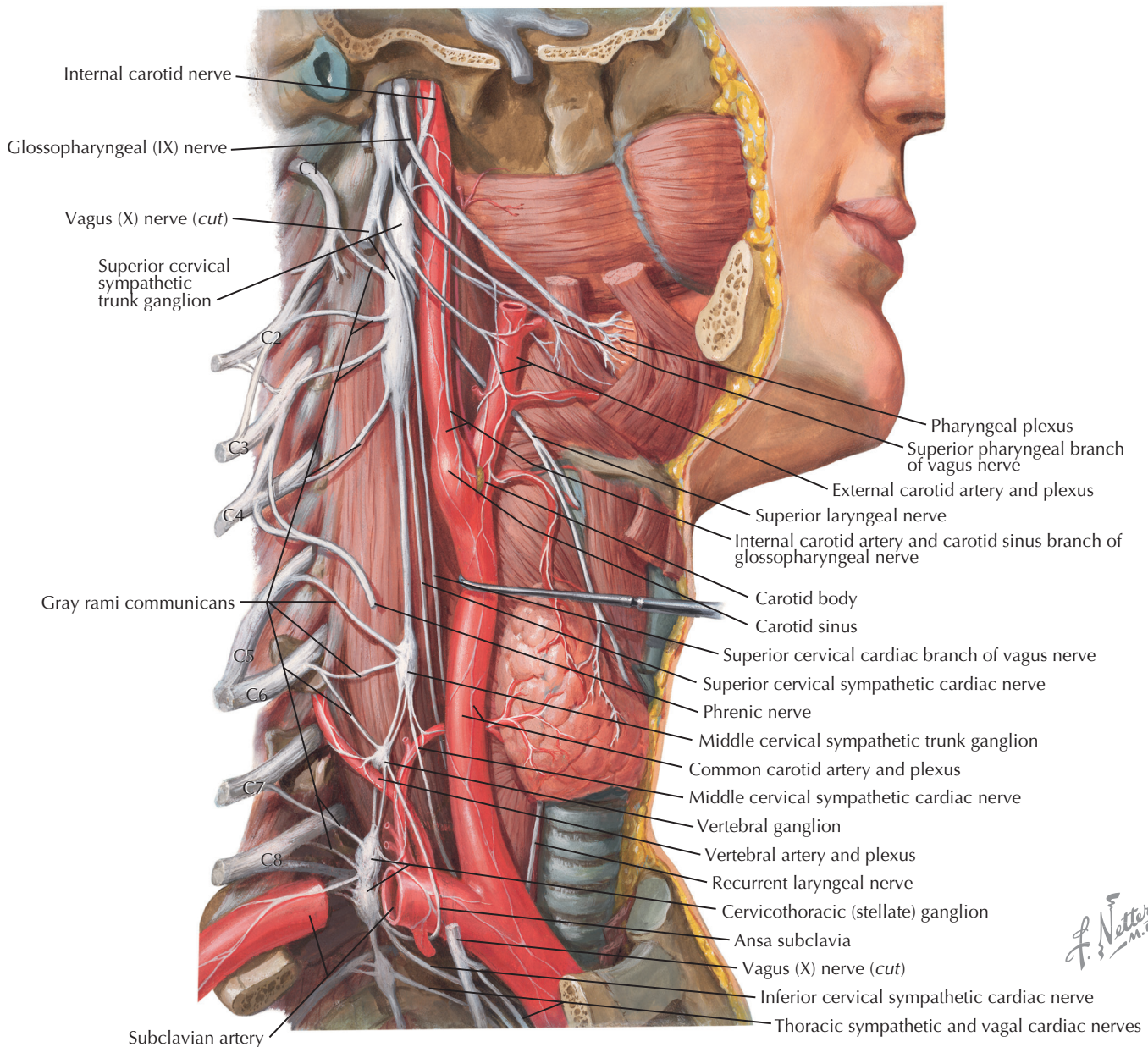
##### CLINICAL POINT

The oculomotor (III nerve) parasympathetic distribution to the eye forms a vital link in one of the most important reflexes in neurology, the pupillary light reflex. Light shone into one eye provides an afferent signal that is processed by the retina, resulting in ganglion cell activation and axonal projections to the pretectum on both sides. The pretectum, through direct and contralateral connections via the posterior commissure, stimulates the nucleus of Edinger-Westphal bilaterally.

This system, via connections in the ciliary ganglion, distributes to the pupillary constrictor muscle, resulting in constriction of the ipsilateral (direct) and contralateral (consensual) pupils. The pupillary light reflex is particularly important in someone with a head injury, intracranial bleed, or space-occupying mass in whom possible brain herniation is suspected. The third nerve may be trapped and compressed against the free edge of the tentorium cerebelli, resulting in failure of the ipsilateral pupil to constrict and disruption of the pupillary light reflex.

The superior cervical ganglion (SCG) is the most rostral component of the sympathetic chain. It supplies structures in the head and neck, including the pupillary dilator muscle, blood vessels, sweat glands, pineal gland, thymus gland, and superior tarsal (Müller's) muscle. The T1–T2 intermediolateral cell column in the spinal cord (preganglionic sympathetic neurons) innervates the SCG; this ganglion then distributes noradrenergic fibers to the pupillary dilator muscle, resulting in dilation of the pupil. When CN III is damaged (e.g., by compression during transtentorial herniation), the actions of the sympathetic SCG are unopposed, resulting in a fixed (unresponsive to the pupillary light reflex), dilated pupil. In circumstances in which the SCG or its central innervation is damaged (e.g., apical lung tumor, Horner's syndrome), the ipsilateral pupil cannot dilate and the pupil is constricted (miotic).

A pupil that constricts when light is shone into one eye and paradoxically appears to dilate when light is shone into the other eye (swinging flashlight test) indicates an afferent (CN II) defect, with the paradoxical dilation occurring as the result of recovery from the initial constriction because of the unresponsiveness of the damaged CN II.



*F. Netter M.D.*

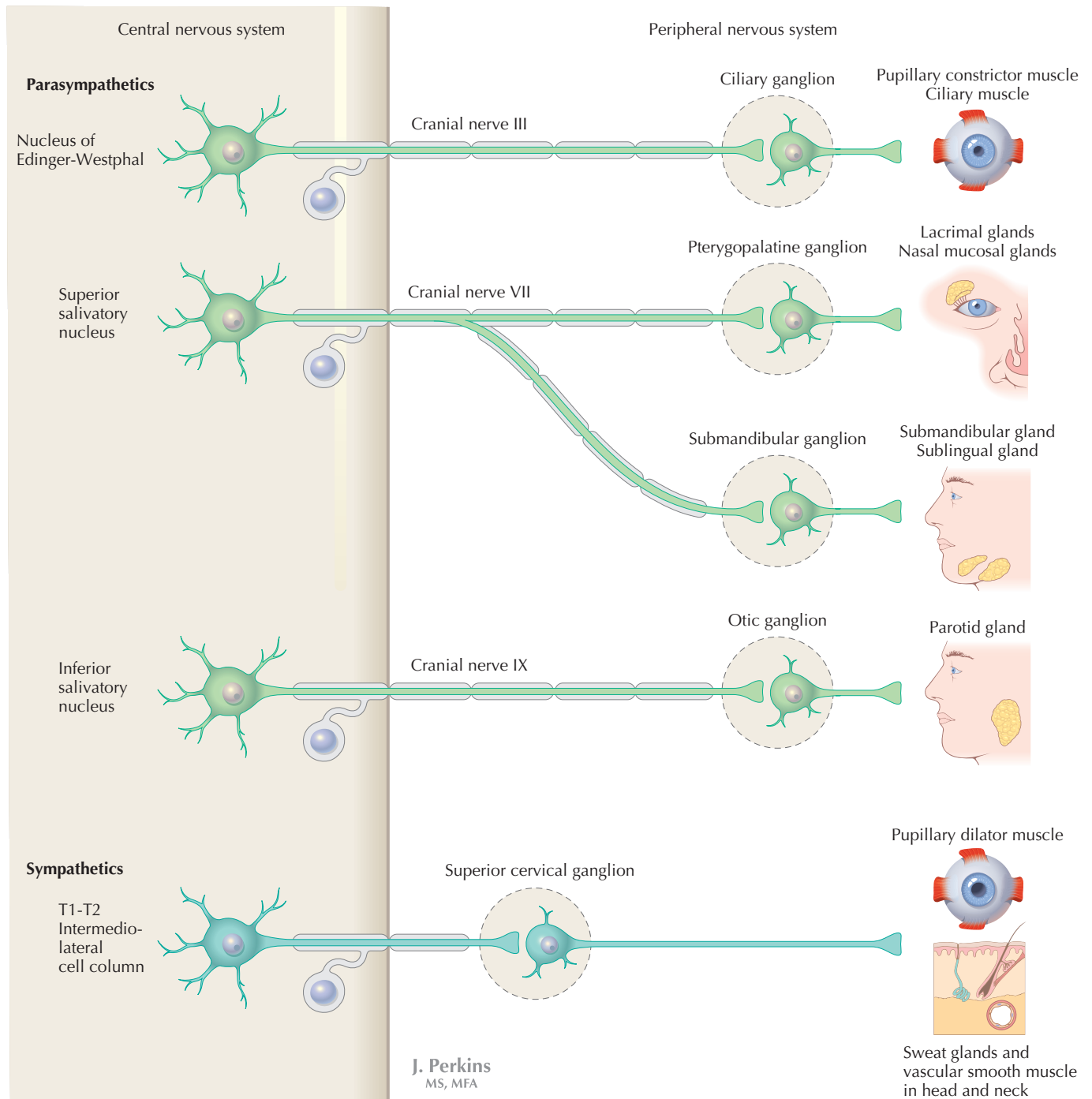
### 9.49 AUTONOMIC DISTRIBUTION TO THE HEAD AND NECK: LATERAL VIEW

The parasympathetic nerve fibers to the head and neck regulate pupillary constriction and accommodation for near vision (CN III, ciliary ganglion to pupillary constrictor muscle and ciliary muscle); tear production (CN VII, pterygopalatine ganglion to lacrimal glands); and salivation (CN VII, submandibular ganglion to submandibular and sublingual glands and CN IX, otic ganglion to parotid gland). The sympathetic nerve fibers to the head and neck derive mainly from the SCG, with synapses to the pupillary dilator muscle, sweat glands, vascular smooth muscle, and the thymus gland.

#### CLINICAL POINT

Blood flow to the brain, derived from the two internal carotid arteries and the two vertebral arteries, is highly regulated. The brain requires moment-to-moment delivery of oxygen and glucose to maintain

cerebral activity and generate the adenosine triphosphate needed for the high energy demands of neurons. Blood flow to the brain is autoregulated; several levels of superimposed control derive from metabolic and neural regulatory systems. (1) Autoregulation may be based on smooth muscle responsiveness to stretch and on endothelial cell response to vasoactive secretory products. (2) Superimposed on autoregulation is metabolic control that is based on blood gases (oxygen, carbon dioxide) and on metabolic products stimulated by neuronal activity (nitric oxide, adenosine, lactate, some ions). (3) A third level of regulation derives from neural regulation. The superior cervical ganglion sends noradrenergic (colocalized with neuropeptide Y) sympathetic vasoconstrictor fibers along the vasculature, and the sphenopalatine ganglion sends acetylcholinergic (colocalized with vasoactive intestinal peptide; VIP) vasodilator fibers along the vasculature. The trigeminal ganglion also distributes substance P (colocalized with calcitonin gene-related peptide) vasodilator fibers along the vasculature; these fibers can be activated by pain. Some central regions, such as the fastigial nucleus of the cerebellum and the rostral ventrolateral medulla, can regulate the activation of some of these neural circuits to the cerebral vasculature, influencing blood flow to the brain.



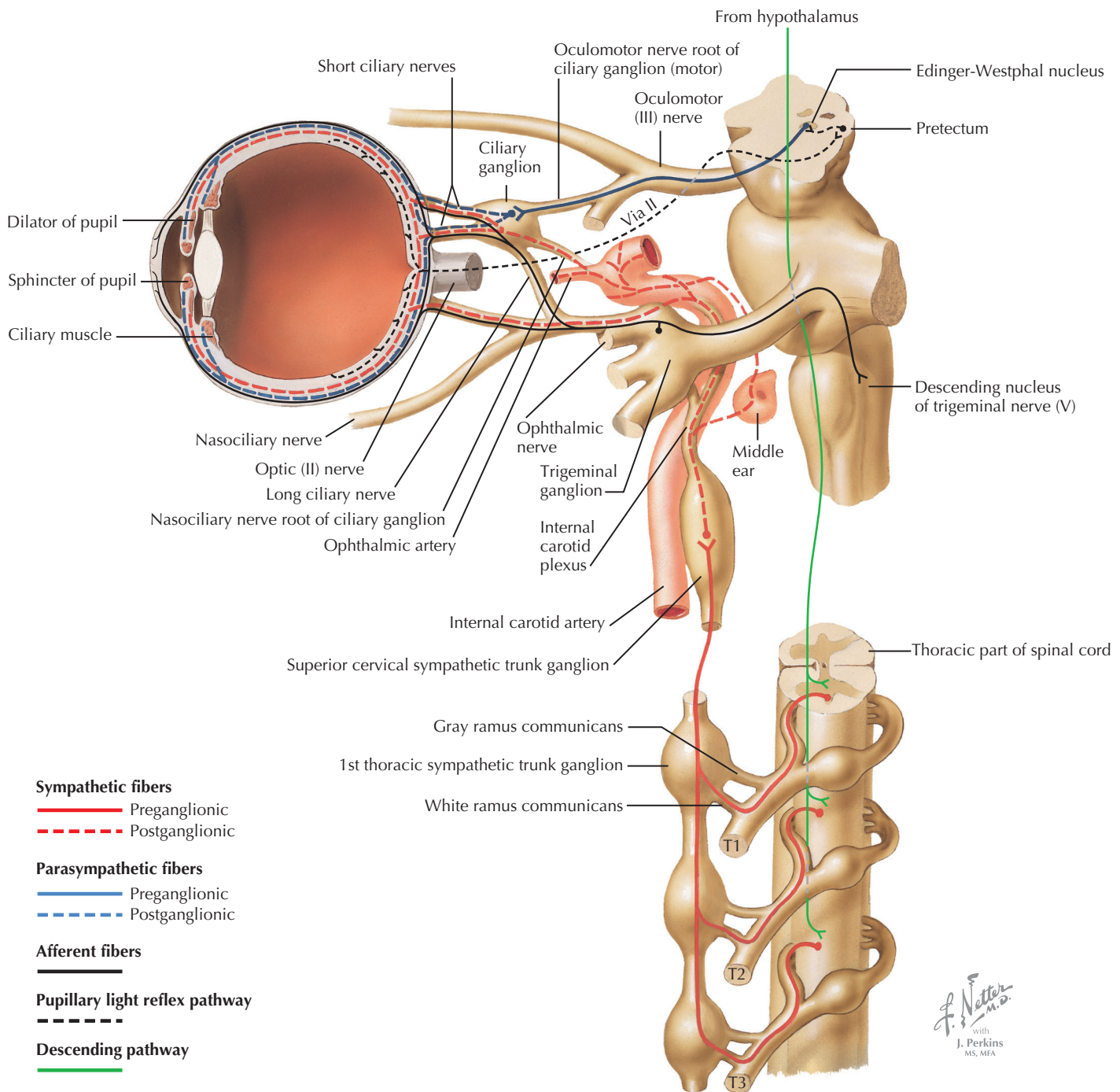
### 9.50 SCHEMATIC OF AUTONOMIC DISTRIBUTION TO THE HEAD AND NECK

Autonomic innervation to the head and neck is derived from parasympathetic neurons in the brain stem, including the nucleus of Edinger-Westphal (CN III), the superior salivatory nucleus (CN VII), and the inferior salivatory nucleus (CN IX), and from sympathetic neurons in the T1–T2 intermediolateral cell column in the spinal cord. The associated ganglia and target (effector) tissue are illustrated.

#### CLINICAL POINT

The superior and inferior salivatory nuclei provide important parasympathetic regulatory control over salivation. The superior salivatory nucleus innervates (via CN VII) the submandibular ganglion, which supplies the submandibular and sublingual glands; the inferior salivatory nucleus innervates (via CN IX) the otic ganglion, which supplies the parotid gland. These parasympathetic fibers stimulate secretion of saliva. In addition, sympathetic innervation from the superior cervical ganglion activates contraction of the myoepithelial cells of the salivary ducts. Salivation is important as an initial phase of the digestion process; it prepares food for swallowing, aids in speaking, and contains mediators and immunoglobulins that provide an initial protective barrier against potentially dangerous organisms that gain access to the oral cavity.

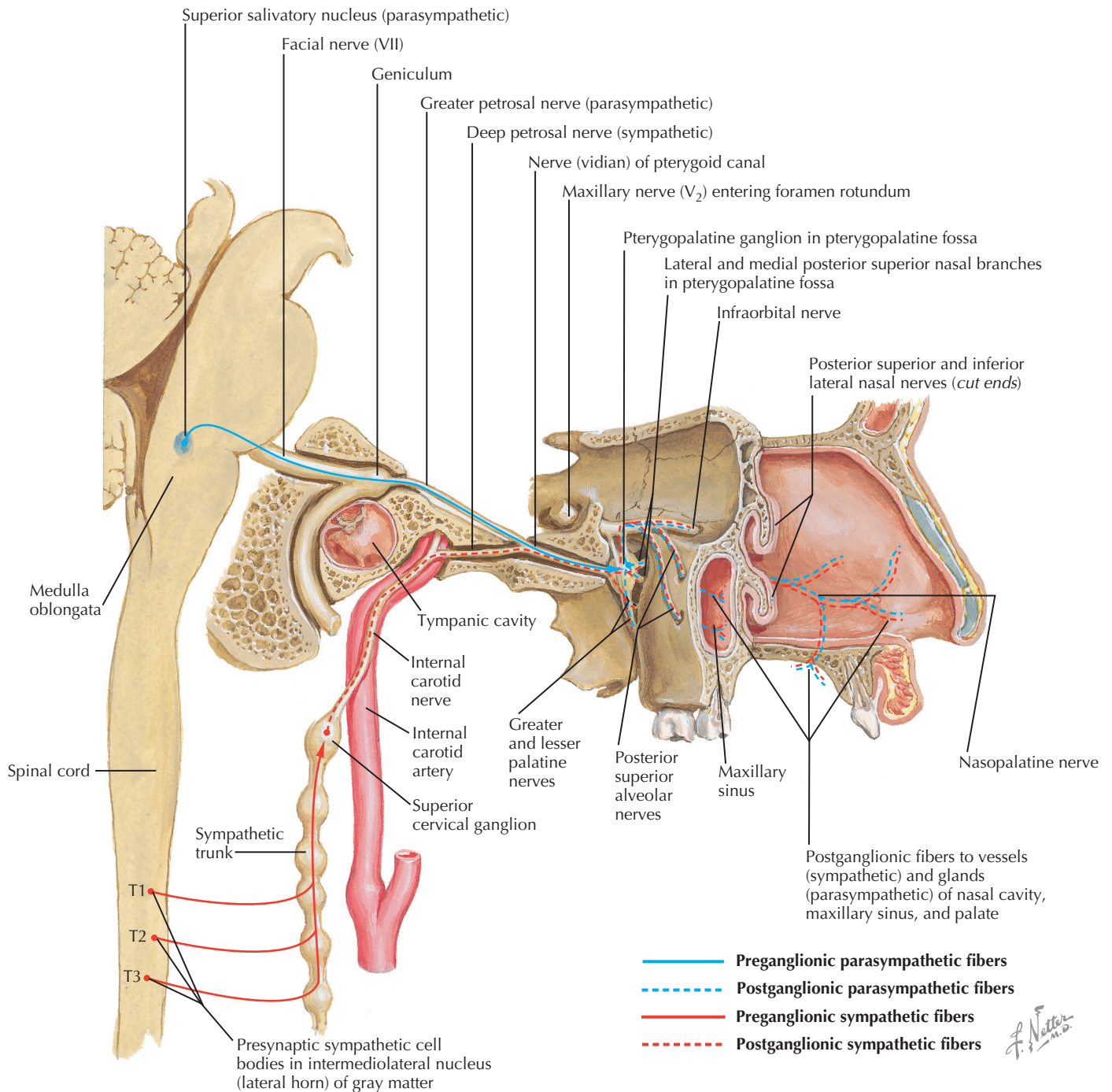




### 9.51 AUTONOMIC DISTRIBUTION TO THE EYE

Parasympathetic preganglionic nerve fibers from the Edinger-Westphal nucleus innervate the ciliary ganglion, which supplies the ciliary muscle (aiding in accommodation to near vision) and the pupillary constrictor muscle (constricting the pupil). Sympathetic preganglionic nerve fibers from the T1–T2 intermediolateral cell column innervate the superior cervical ganglion, which supplies the dilator muscle of the pupil.

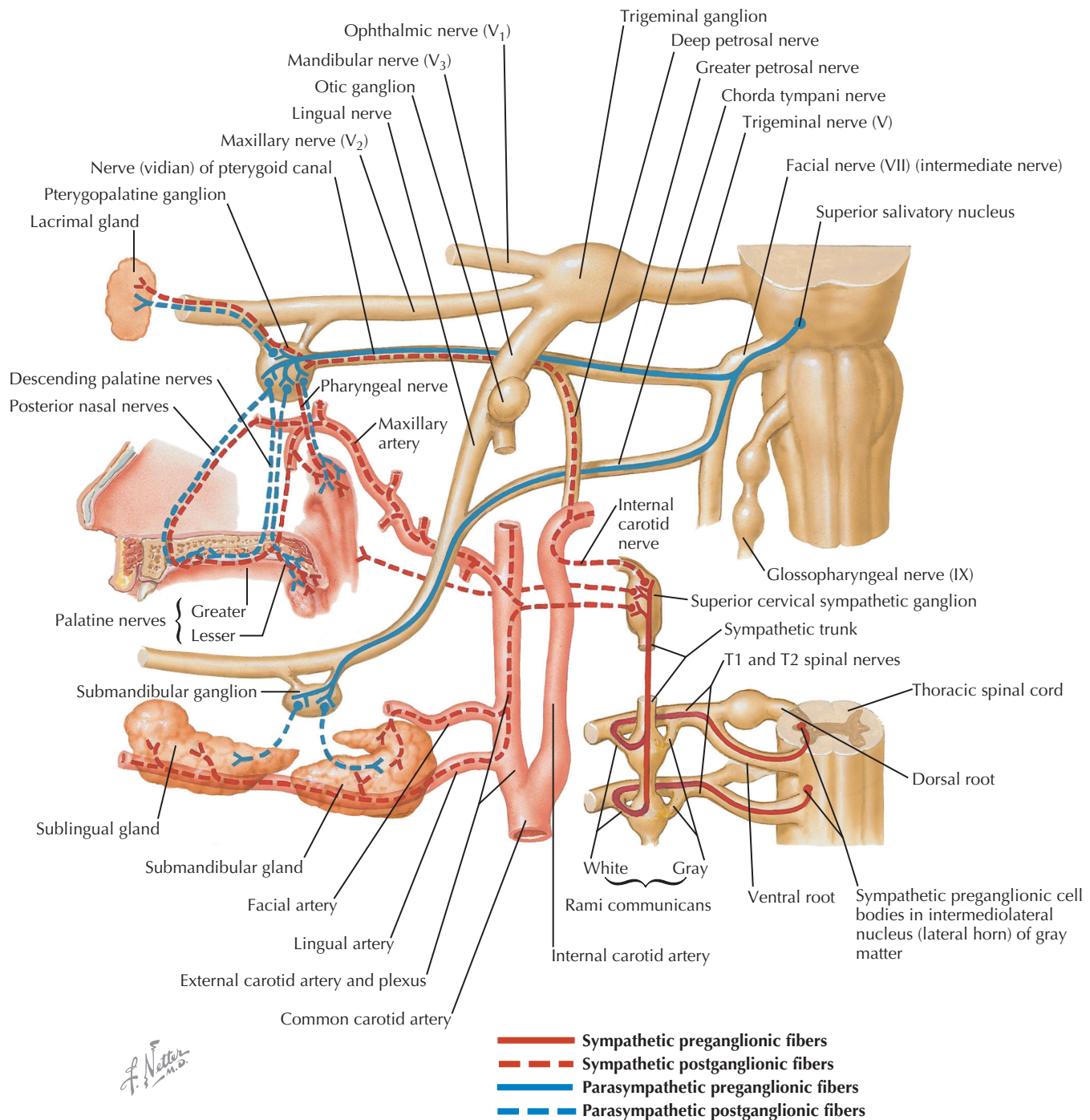
The pupillary light reflex is a major reflex in neurological testing. The afferent limb is activated by light shone in either eye via CN II and processed through the pretectum to the Edinger-Westphal nucleus on both sides (via the posterior commissure); the efferent limb consists of autonomic parasympathetic outflow to the pupillary constrictor muscles of both sides.



### 9.52 AUTONOMIC INNERVATION OF THE NASAL CAVITY

Parasympathetic preganglionic neurons in the superior salivatory nucleus innervate the pterygopalatine ganglion. Sympathetic preganglionic neurons from the T1–T2 interme-

diolateral cell column innervate the SCG. The pterygopalatine ganglion supplies secretory glands, and the SCG supplies blood vessels with postganglionic nerve fibers in the nasal cavity, maxillary sinus, and palate.

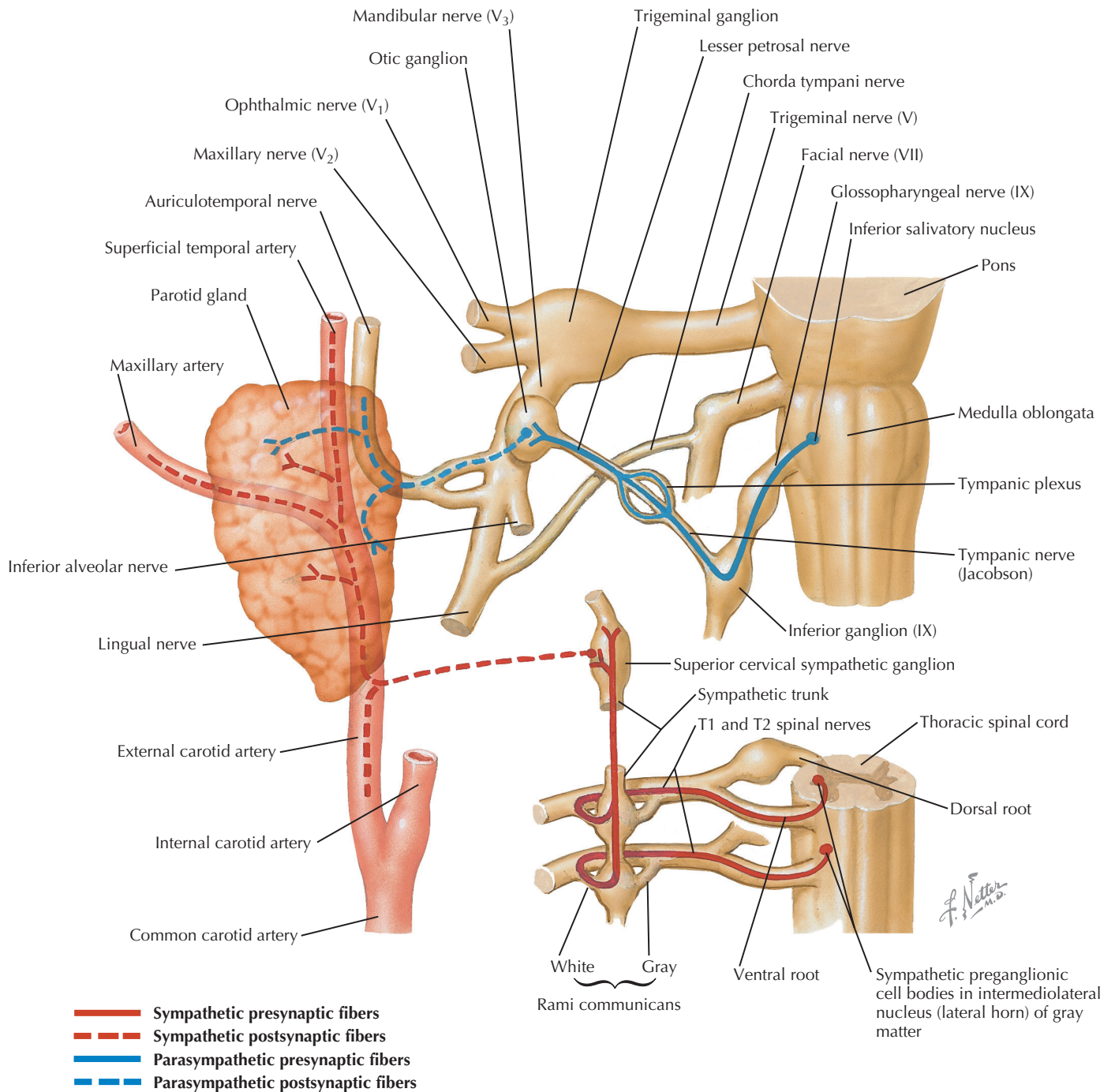


### 9.53 SCHEMATIC OF THE PTERYGOPALATINE AND SUBMANDIBULAR GANGLIA

The pterygopalatine and submandibular ganglia, innervated by the superior salivatory nucleus via CN VII, supply the lac-

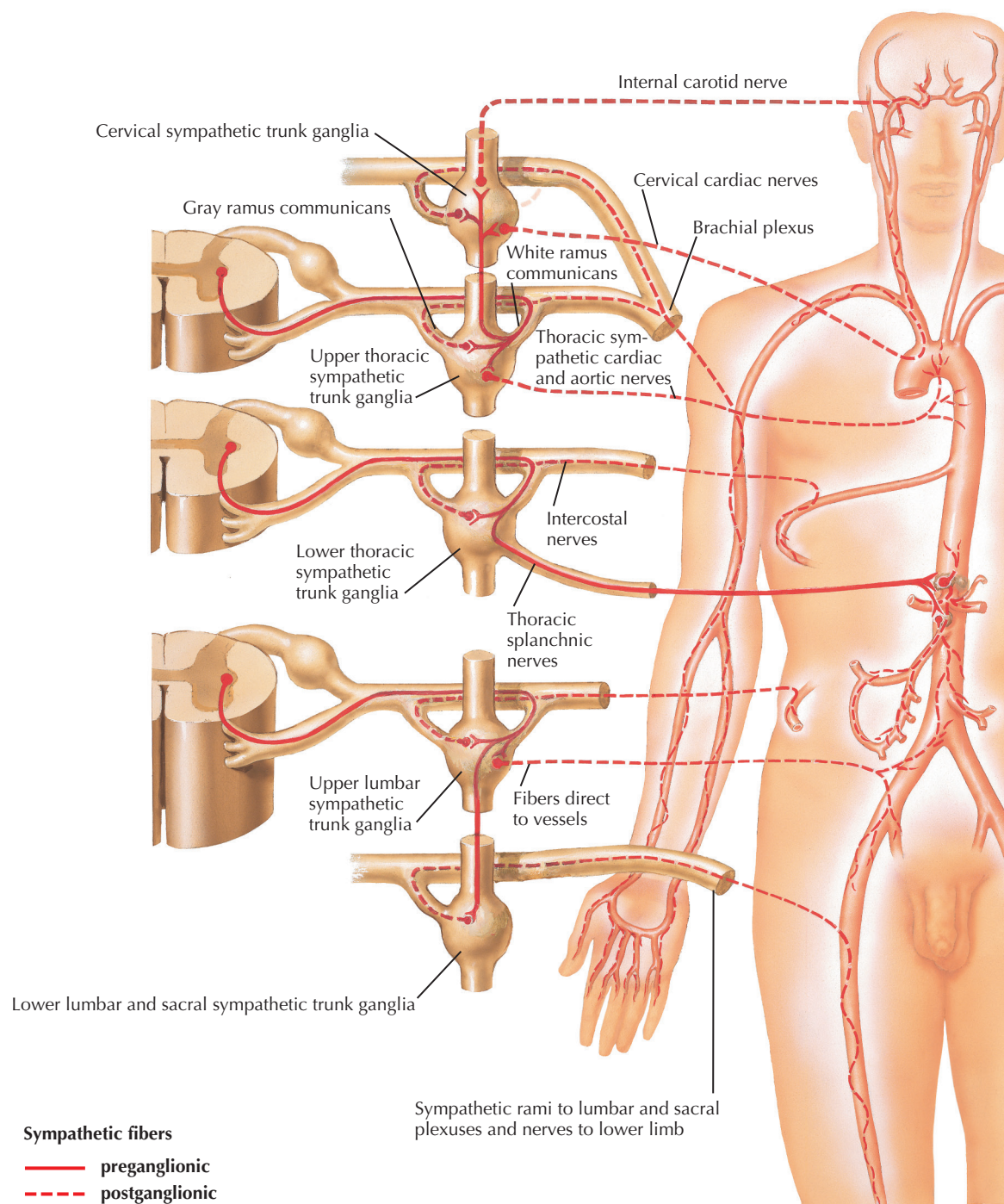
rimal glands and nasal mucosal glands as well as the submandibular and sublingual salivary glands, respectively, with postganglionic parasympathetic cholinergic nerve fibers.





### 9.54 SCHEMATIC OF THE OTIC GANGLION

The otic ganglion, innervated by the inferior salivatory nucleus via CN IX, supplies the parotid salivary gland with postganglionic parasympathetic cholinergic nerve fibers.

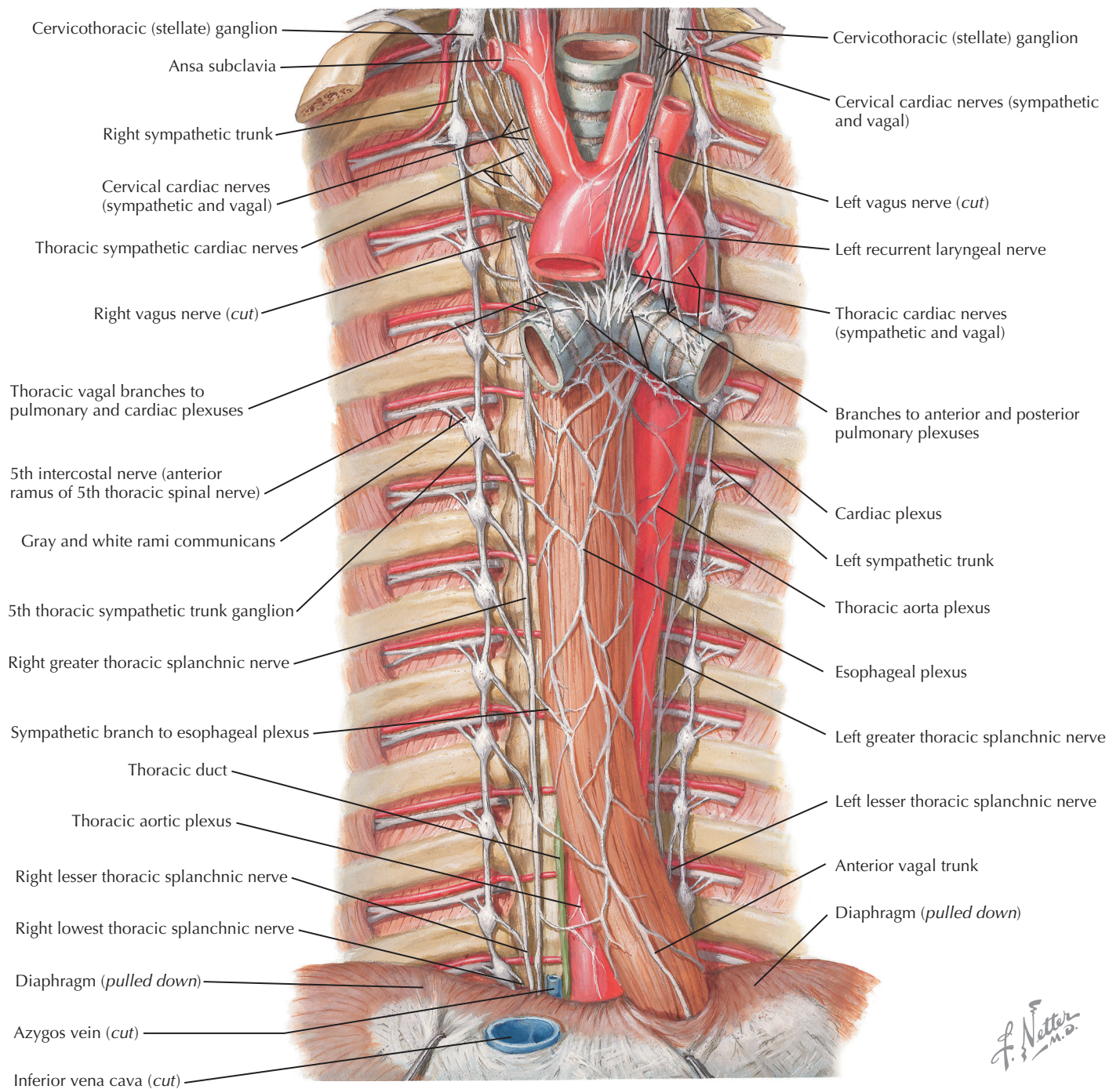


### 9.55 INNERVATION OF THE LIMBS

Autonomic innervation to the limbs derives from the SNS. Preganglionic sympathetic nerve fibers from the thoracolumbar intermediolateral cell column supply sympathetic chain ganglia. These ganglia send postganglionic noradrenergic nerve fibers through the gray rami communicans into the

peripheral nerves to supply vascular smooth muscle (vasomotor fibers), sweat glands (sudomotor fibers), and arrector pili muscles associated with hair follicles (pilomotor fibers). Smooth muscle fibers of blood vessels in the viscera also are supplied with postganglionic sympathetic nerve fibers.





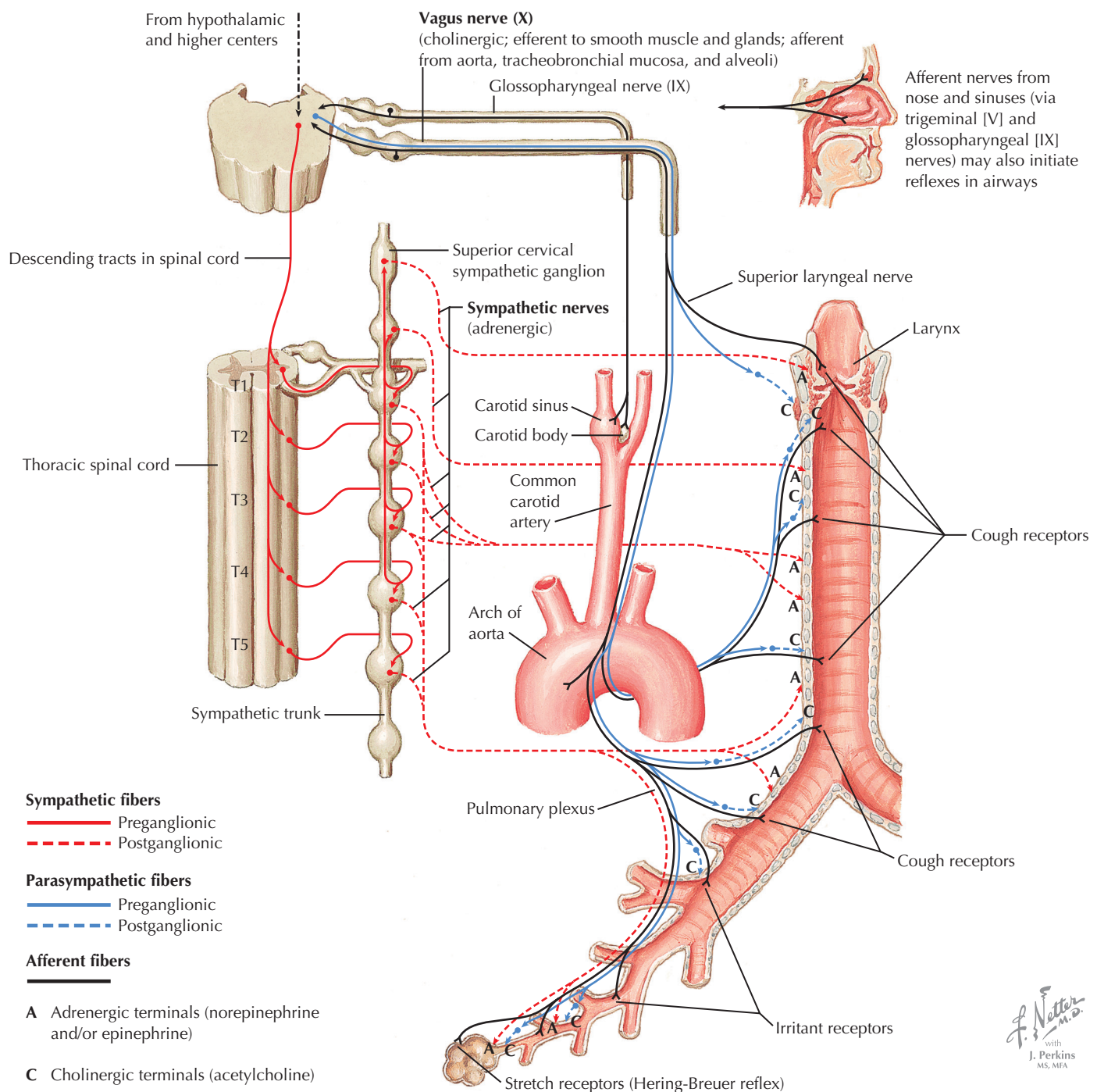
### 9.56 THORACIC SYMPATHETIC CHAIN AND SPLANCHNIC NERVES

The sympathetic chain is a collection of sympathetic ganglia that receive input from the thoracolumbar preganglionic nerve fibers derived from the spinal cord. The ganglia, interconnected by nerve trunks, are located in a paravertebral array from the neck to the coccygeal region. Postganglionic noradrenergic nerve fibers from the sympathetic chain supply effector tissue in the periphery. Some preganglionic nerve fibers do not synapse as they travel through the sympathetic chain. They continue along the splanchnic nerves to synapse in collateral ganglia, which supply noradrenergic innervation to effector tissue in the viscera.

#### CLINICAL POINT

The sympathetic chain (paravertebral ganglia) extends from the neck to the pelvis, whereas collateral (prevertebral) ganglia are present along the great vessels and distribute to internal target organs. These ganglia are supplied by preganglionic cholinergic fibers from the T1–L2 intermediolateral cell column (lateral horn), the chain ganglia via white rami communicans, and the collateral ganglia via splanchnic nerves. A spinal cord crush injury above the T1 level damages the central regulation of the sympathetic preganglionic neurons and the parasympathetic S2–S4 preganglionic neurons. Initially the patient experiences a spinal shock syndrome, with hypotension (worse on standing), loss of sweating, loss of piloerection, paralysis of bladder function (neurogenic bladder), gastric dilatation, and paralytic ileus. As the process of spinal cord injury resolves to a permanent state and spinal shock recedes, the autonomic equivalent of spasticity (hyper-responsiveness) may result, accompanied by spikes in blood pressure and a spastic bladder.



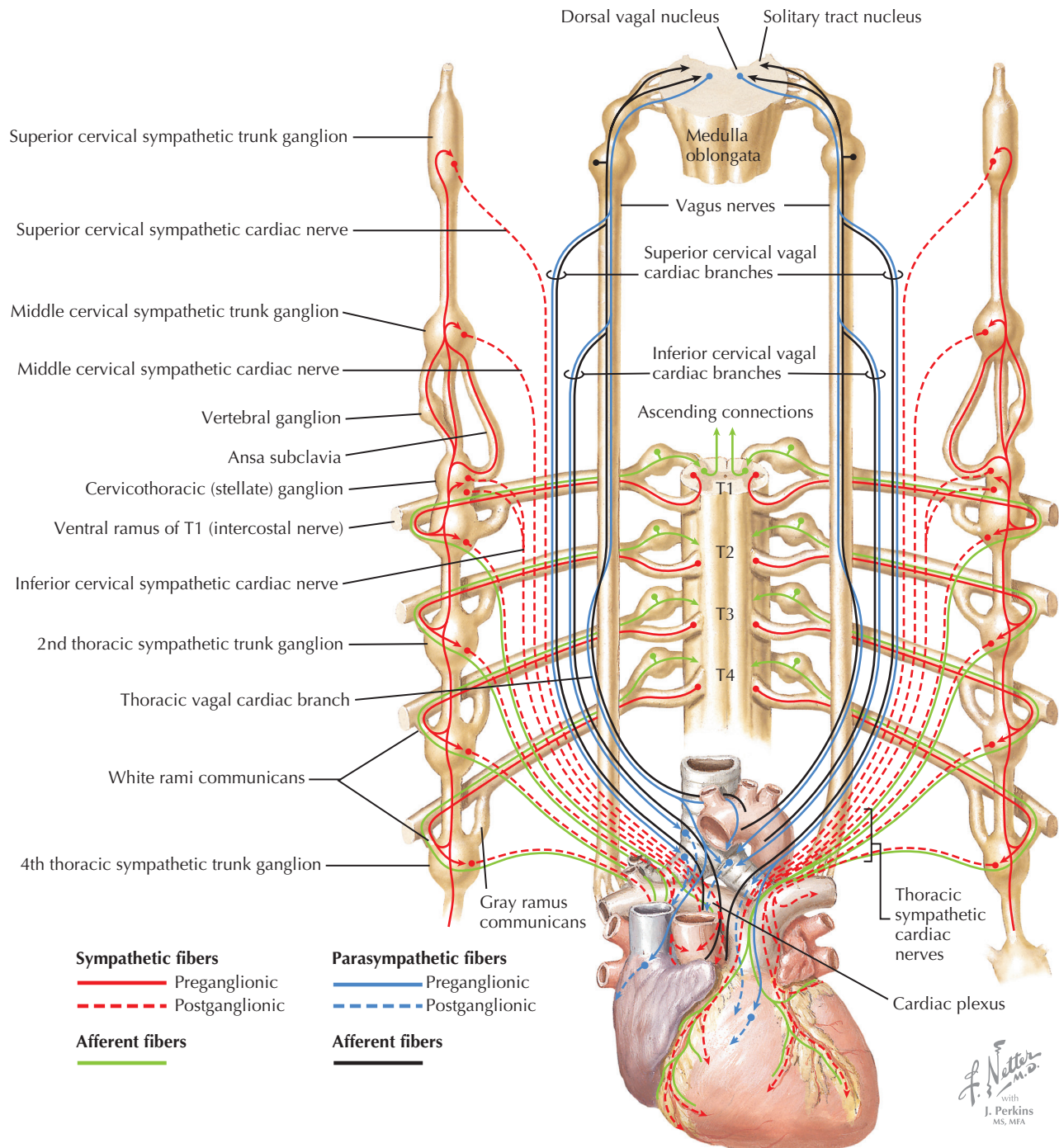


*F. Netter M.D.*  
with  
J. Perkins  
MS, MFA

### 9.57 INNERVATION OF THE TRACHEOBRONCHIAL TREE

Both sympathetic (noradrenergic) and parasympathetic (cholinergic) innervation supplies smooth muscle of the tracheobronchial tree. Sympathetics derive from the sympathetic chain, and parasympathetics derive from vagal autonomic input to local intramural ganglia. Sympathetic influences result in bronchodilation and parasympathetic influences

result in bronchoconstriction. Some medications for asthma use a sympathomimetic compound; others use a parasympathetic blocker. Additional neuropeptidergic innervation, some as colocalized or independent autonomic fibers and some as primary afferent fibers, also distributes along the epithelium and among the alveoli, where they can influence innate immune reactivity and the production of inflammatory mediators.



*F. Netter M.D.*  
with  
J. Perkins  
MS, MFA

### 9.58 INNERVATION OF THE HEART

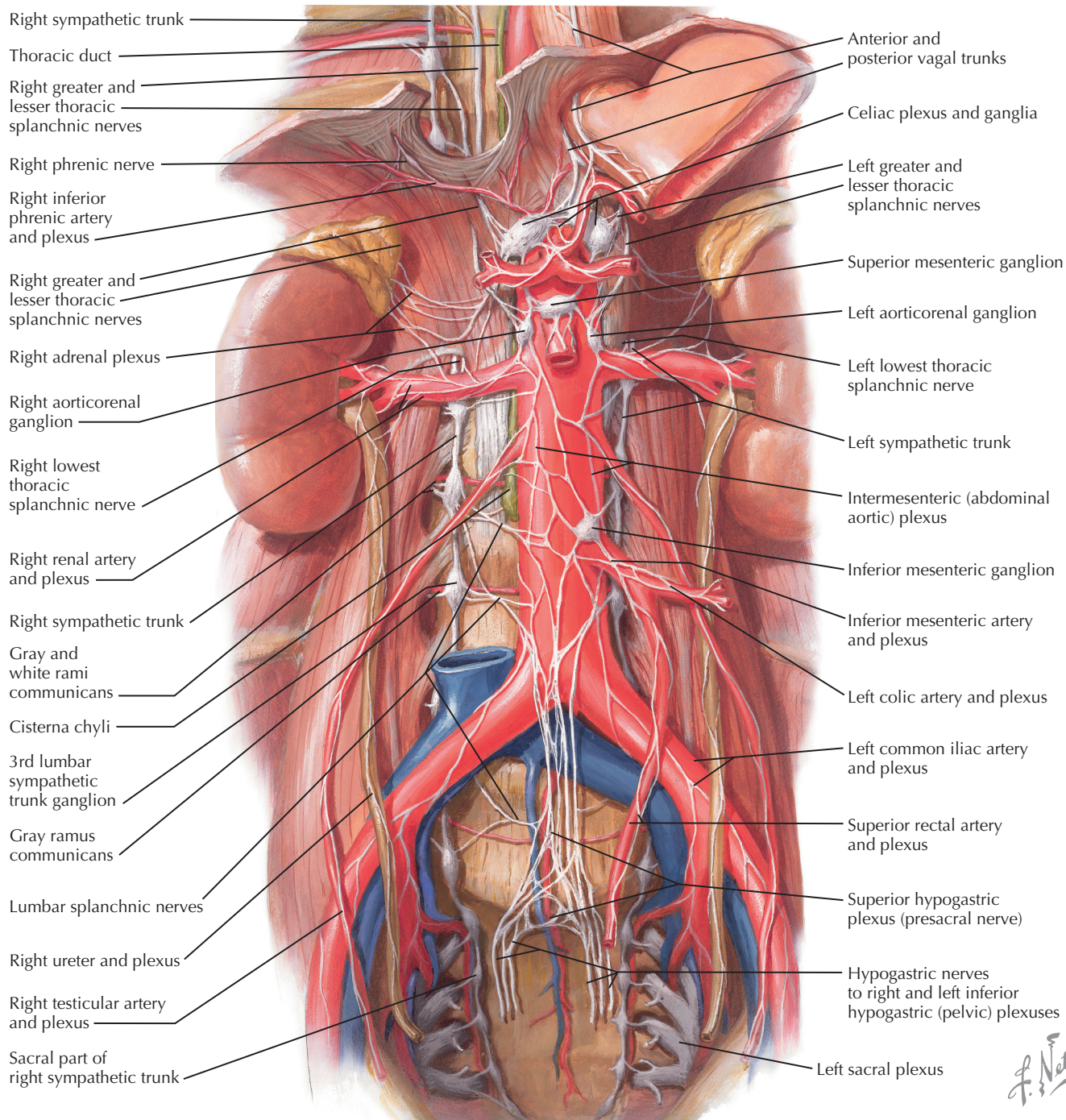
Sympathetic noradrenergic nerve fibers (derived from chain ganglia) and parasympathetic cholinergic nerve fibers (derived from cardiac intramural ganglia innervated by the vagus nerve) supply the atria, ventricles, sinoatrial node, and atrioventricular node and bundle. Sympathetic noradrenergic nerve fibers also distribute along the great vessels and the coronary arteries. Sympathetic fibers increase the force and rate of cardiac contraction, increase cardiac output, and dilate the coronary arteries. Parasympathetic fibers decrease the force and rate of cardiac contraction and decrease cardiac output.

#### CLINICAL POINT

Both sympathetic noradrenergic and parasympathetic cholinergic vagal postganglionic fibers innervate the heart. Cardiovascular auto-

nomic neuropathies sometimes occur in diabetes and other disorders. Vagal nerve damage can result in sustained tachycardia; excessive vagal activity can provoke bradycardia, atrial fibrillation or flutter, ventricular fibrillation, or paroxysmal tachycardia. Loss of sympathetic innervation of the heart results in severe exercise intolerance, painless myocardial ischemia, cardiomyopathy, and possibly sudden death. In studies of cardiac failure, the increased reflex drive on sympathetic cardiac nerves in an attempt to increase cardiac output results in accelerated release of norepinephrine, which produces highly toxic oxidative metabolites (free radicals) that are taken up by the noradrenergic nerve endings (through the high-affinity uptake carriers) and produce a dying-back sympathetic neuropathy, leaving the heart further denervated. In experimental models in dogs, either a norepinephrine-specific uptake inhibitor (desmethylinipramine) or potent antioxidants (vitamins C and E) can prevent this free-radical autodestructive process.





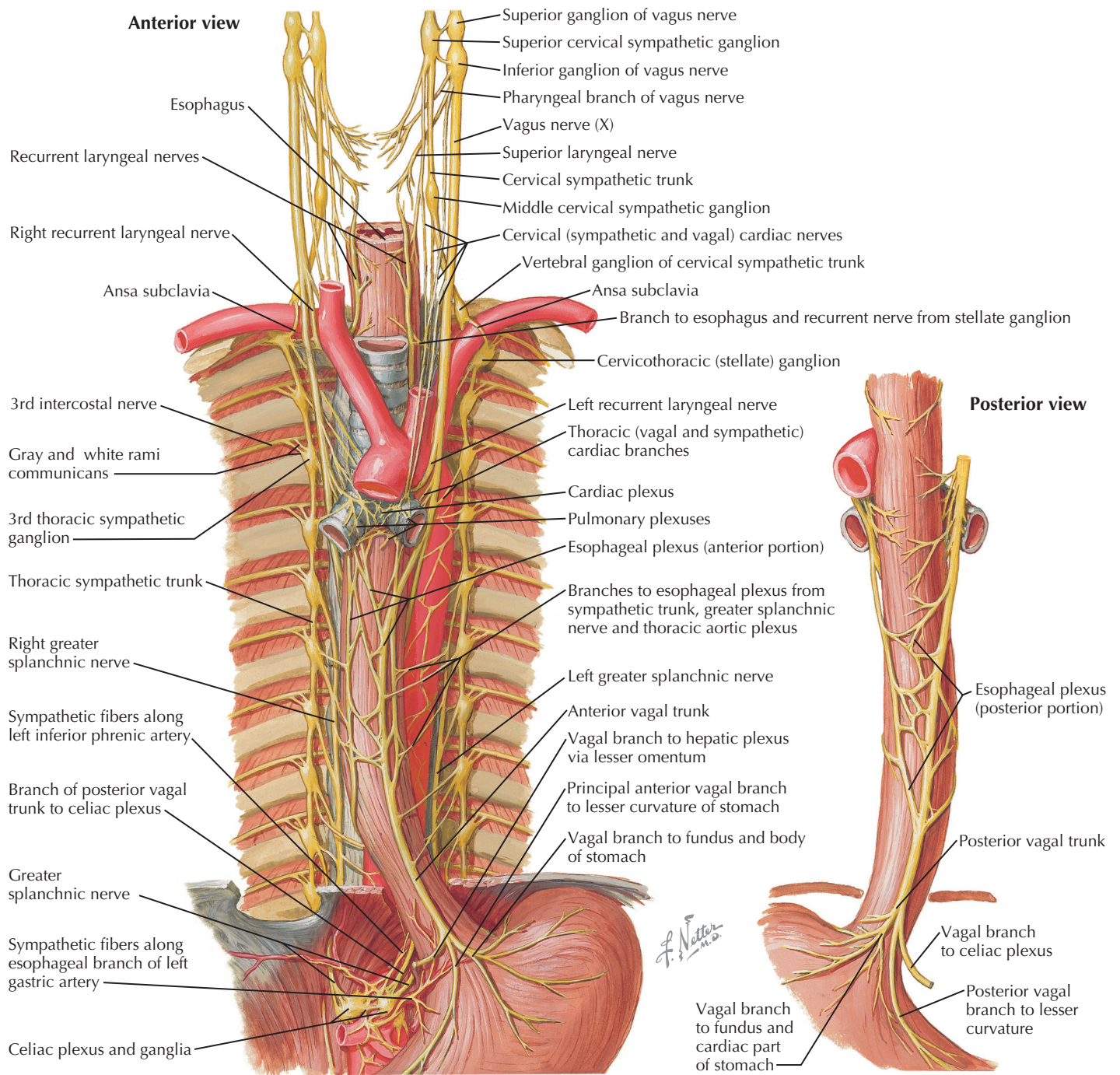
### 9.59 ABDOMINAL NERVES AND GANGLIA

Abundant sympathetic nerves are present in the abdomen and pelvis and are associated with innervation of the gastrointestinal and urogenital systems, associated vessels, the peritoneum, and the adrenal gland. The lumbar portion of the sympathetic chain and its branches and the splanchnic nerves and their collateral ganglia (celiac, superior and inferior mesenteric, hepatic, aorticorenal, adrenal, superior hypogastric, and others) innervate smooth muscle, glands, lymphoid tissue, and metabolic cells in the abdomen and pelvis. Most of the collateral ganglia (plexuses) also contain parasympathetic contributions from the vagus nerve and associated ganglia.

#### CLINICAL POINT

The collateral ganglia (celiac, superior and inferior mesenteric, hepatic, aorticorenal, adrenal, superior hypogastric) and the lumbar sympathetic chain supply sympathetic innervation to the abdomen and pelvis. Parasympathetic vagal fibers and their associated intramural ganglia provide parasympathetic innervation. The importance of this innervation is illustrated by the relatively unusual disorder known as dysautonomic polyneuropathy, which is a postganglionic polyneuropathy of both sympathetic and parasympathetic nerves, most likely the result of autoimmune reactivity. The affected individual develops orthostatic hypotension, unresponsive pupillary light reflexes, paralytic ileus and constipation, bladder dysfunction, and diminished sweating, peripheral vasoconstriction, and piloerection.

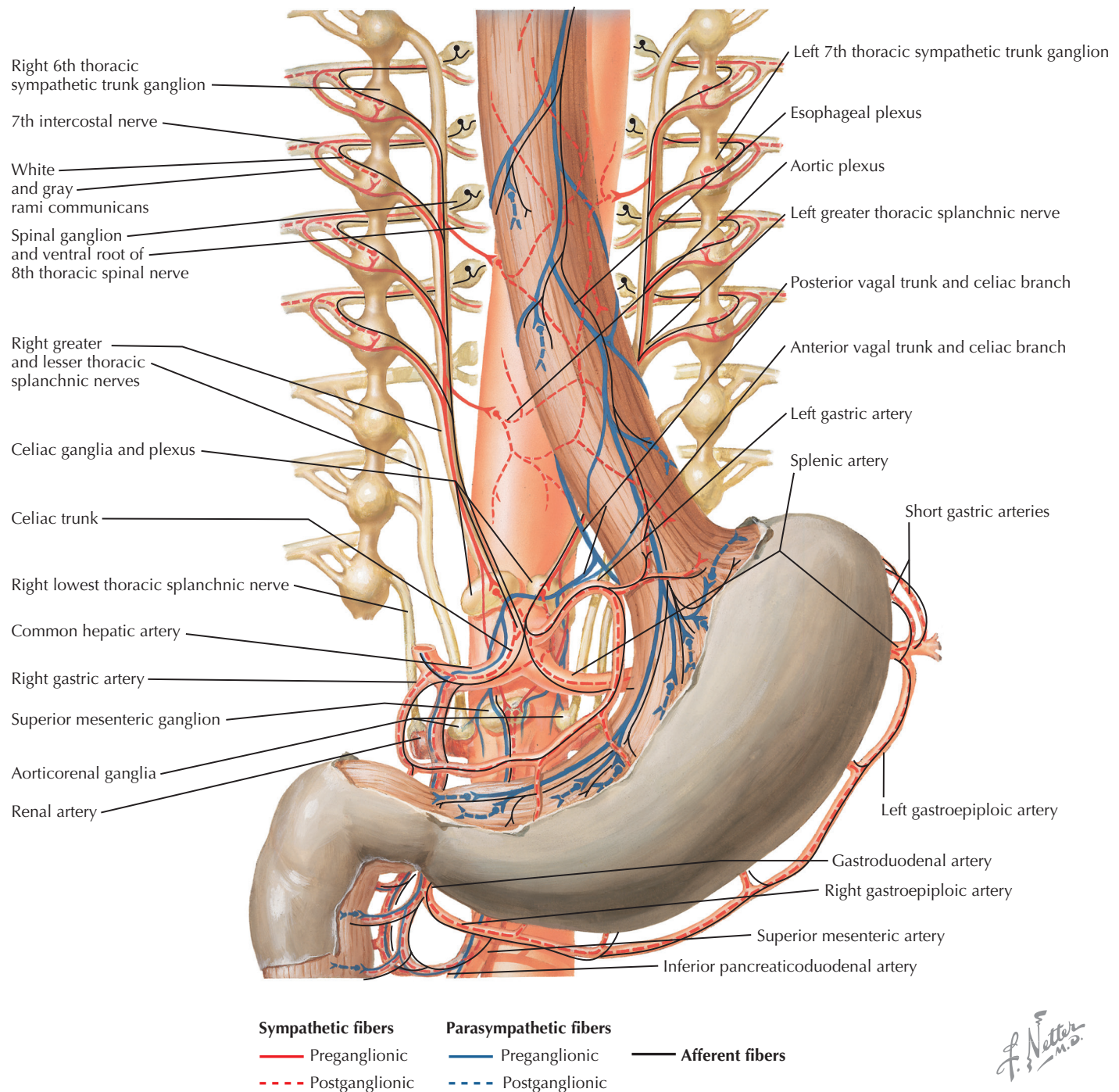




### 9.60 NERVES OF THE ESOPHAGUS

The sensory stimuli that initiate swallowing derive mainly from CN IX (some also from CNs V and X) and are mediated through nucleus solitarius in the medulla. Food passes through the cricopharyngeal sphincter at the proximal esophagus; this sphincter is controlled by the vagal nerve fibers derived from the dorsal motor nucleus of CN X. Movement of food through the esophagus is regulated by vagal nerve fibers derived from

the dorsal motor nucleus of CN X, which synapse on neurons within the myenteric plexus of the esophagus. This plexus directly controls peristalsis through the esophagus by alternately relaxing and then contracting the muscles of the esophagus. Food then moves into the stomach through the lower esophageal sphincter, which relaxes when nitric oxide and VIP are released from some neurons of the myenteric plexus.



### 9.61 INNERVATION OF THE STOMACH AND PROXIMAL DUODENUM

The stomach and proximal duodenum receive abundant sympathetic innervation from the celiac and superior mesenteric ganglia and, to a lesser extent, from the thoracic sympathetic trunk ganglia. The celiac and superior mesenteric ganglia receive their preganglionic input from the greater and lesser thoracic splanchnic nerves. Parasympathetic fibers distribute to the stomach and proximal duodenum from the celiac branches of the vagus nerve. Sympathetic fibers decrease peristalsis and secretomotor activities. Parasympathetic fibers

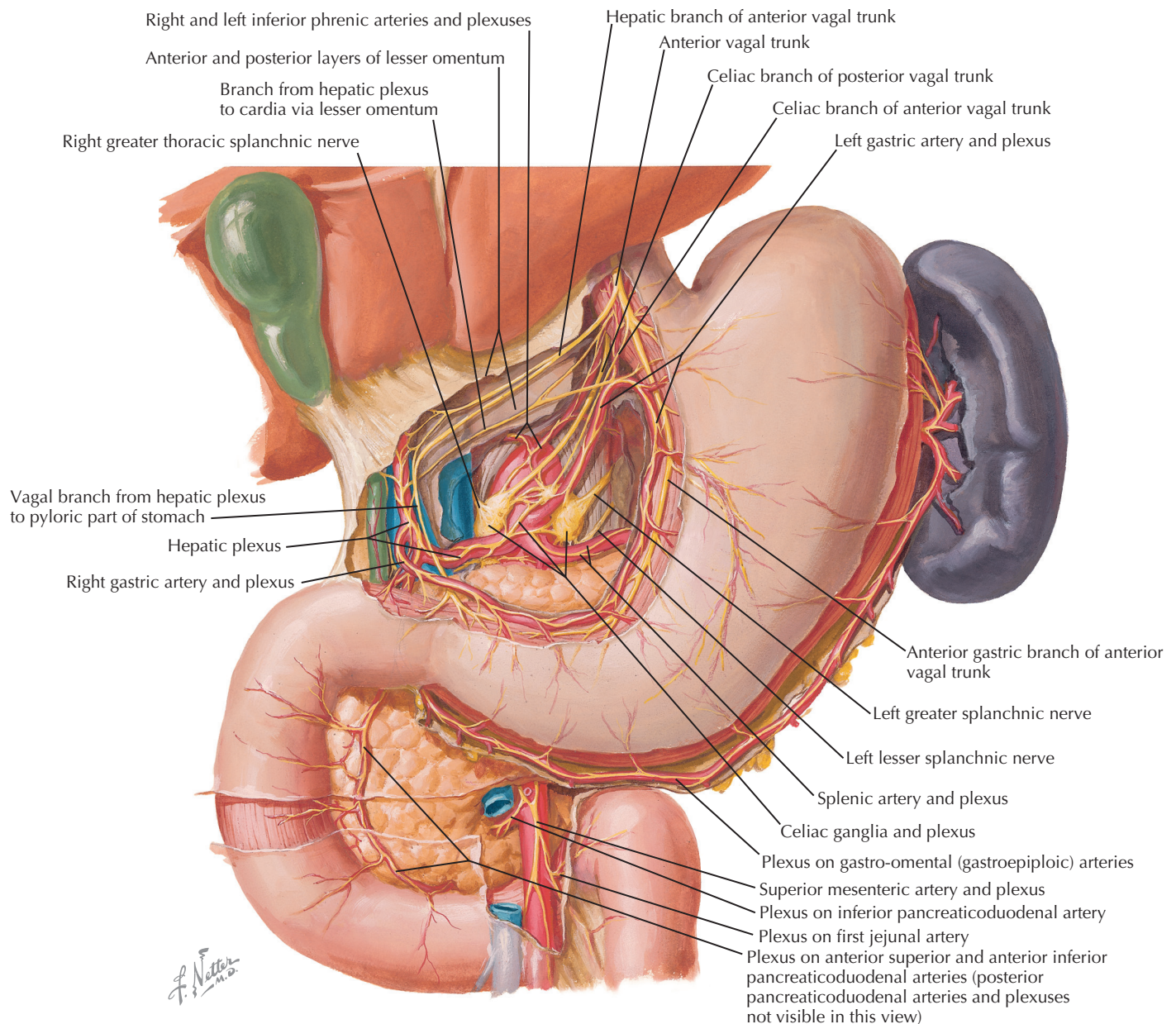
increase peristalsis and secretomotor activity (such as gastrin and hydrochloric acid) and relax associated sphincters.

#### CLINICAL POINT

Diabetic neuropathy may be accompanied by delayed gastric emptying. The patient may experience nausea and vomiting, premature satiety, and large fluctuations in blood glucose. Weight loss may be noted. Approaches for treatment include parasympathetic agonists that stimulate gastric emptying and dopamine antagonists that remove the dopaminergic inhibition of gastric emptying. Delayed gastric emptying may also be accompanied by dysfunction of esophageal motility, resulting in dysphagia.

*F. Netter M.D.*





### 9.62 NERVES OF THE STOMACH AND DUODENUM

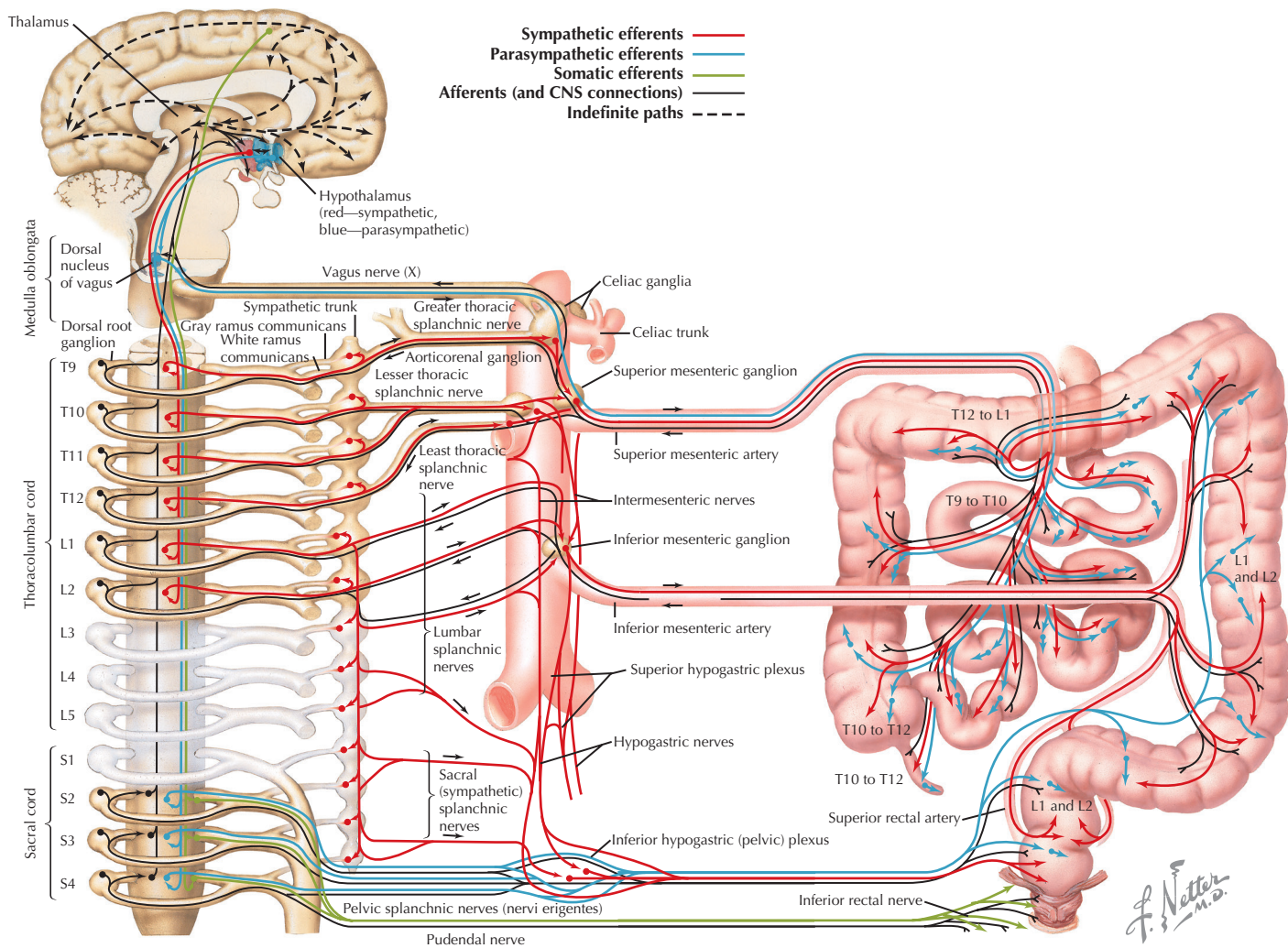
Parasympathetic and sympathetic nerve fibers distribute to the stomach and proximal duodenum through specific splanchnic nerves and branches of the vagus nerve. Sympathetic fibers decrease peristalsis and secretomotor activities. Parasympathetic fibers increase peristalsis and secretomotor activity (such as gastrin and hydrochloric acid) and relax associated sphincters.

#### CLINICAL POINT

Obesity may occur for a variety of reasons. The stomach expands, neural satiety signals do not provide effective feedback to the brain, and compulsive eating can overcome normal appetitive control mechanisms. In situations in which diet and exercise are ineffective for weight control and when diabetes and other serious comorbidities are life-threatening for a morbidly obese individual, bariatric surgery is

an option. The Roux-en-Y gastric bypass procedure takes the distal 90% of the stomach, the duodenum, and approximately 20 cm of the proximal jejunum off-line; the digestive tract then consists of the esophagus and a very small proximal stomach pouch that is connected with the remaining jejunum (the off-line jejunum is anastomosed farther downstream). This procedure markedly reduces the stomach's capacity, slows gastric emptying, and produces deliberate partial malabsorption. Long-term data indicate extensive and permanent weight loss in many subjects (more than 70% of needed weight loss) and common reversal of diabetes, hypertension, sleep apnea, and many of the comorbid conditions that accompany morbid obesity. In addition, a striking alteration in the secretion of a variety of gastrointestinal hormones, inflammatory mediators, and other mediators has been noted. Autonomic and somatic neural signals are altered, central set-points related to appetitive behavior are reset, and changes in morbidity and mortality rates have been observed. The Roux-en-Y procedure is not without risks and complications, and chronic supplementation of nutrients such as calcium, iron, and B vitamins is required. Underlying psychopathology may lead to circumvention of the effectiveness of the procedure.

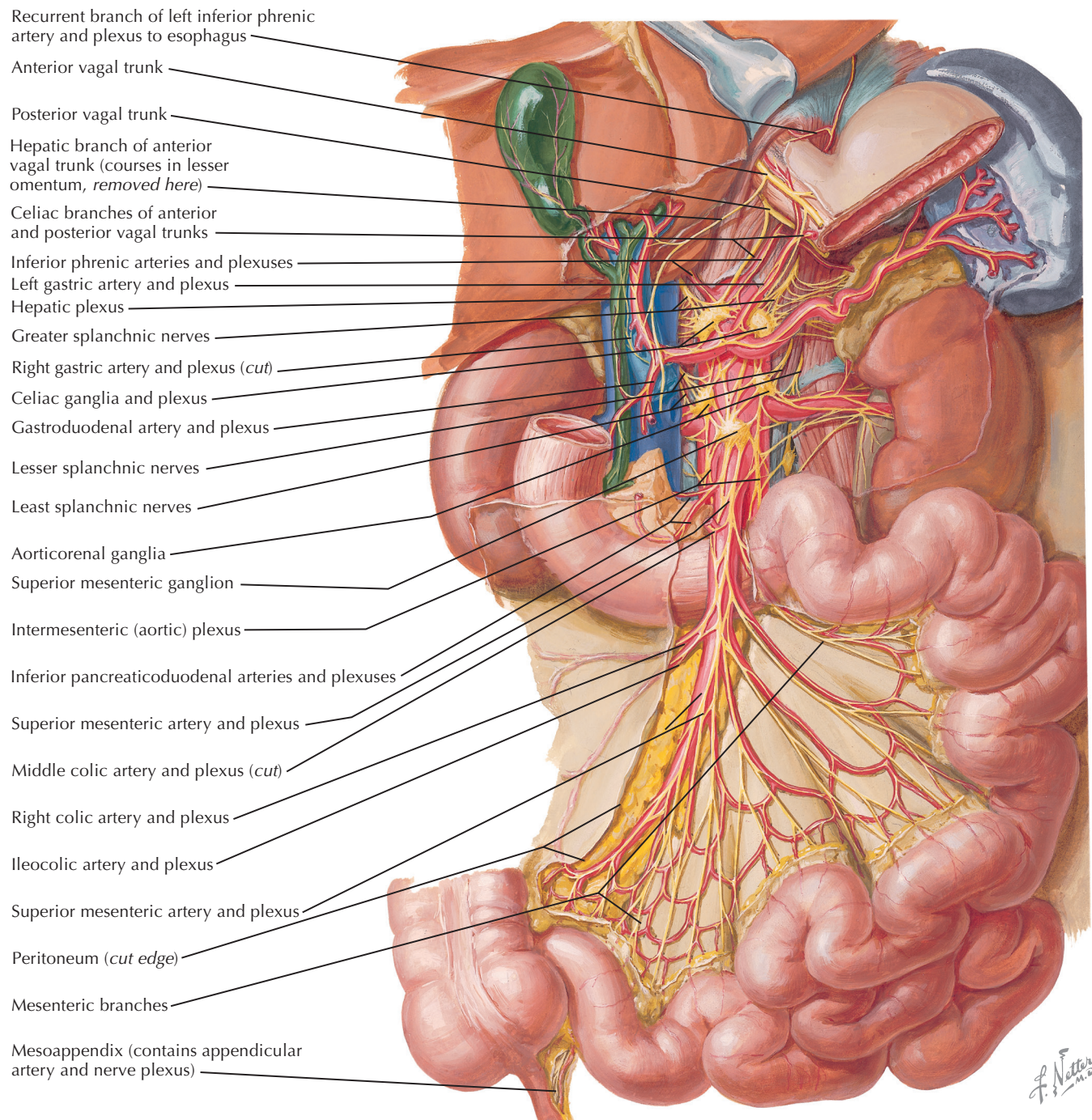




### 9.63 INNERVATION OF THE SMALL AND LARGE INTESTINES

Autonomic innervation of the small and large intestines is supplied by extrinsic sympathetic and parasympathetic fibers. Sympathetic innervation derives from the T5–L2 intermediolateral cell column of the spinal cord and distributes to collateral ganglia (superior and inferior mesenteric, celiac). Parasympathetic innervation derives from the vagus nerve and from the S2–S4 intermediate gray of the spinal cord; it distributes to intramural ganglia and plexuses via CN X and pelvis splanchnic nerves. Sympathetic nerve fibers generally

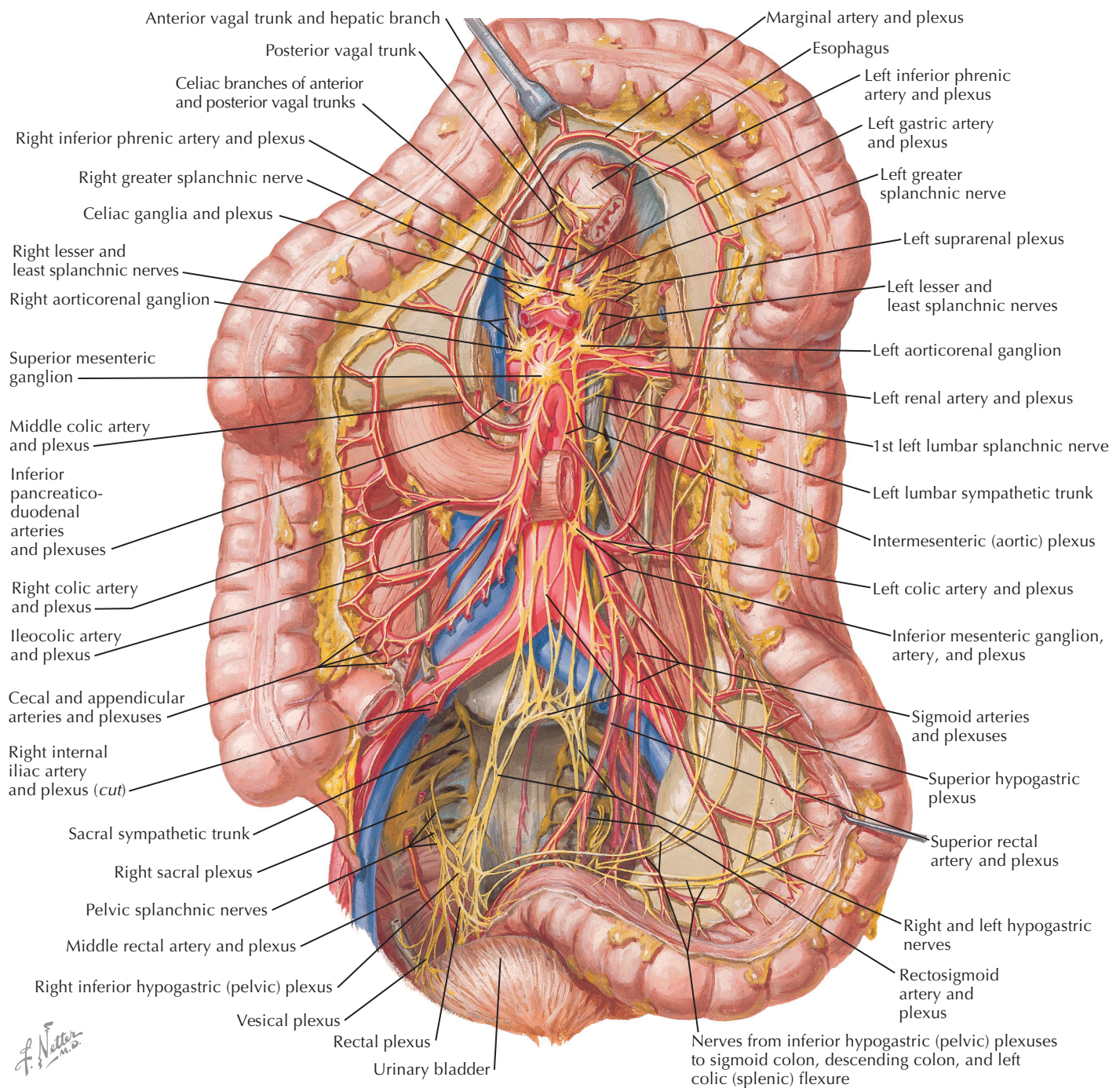
decrease peristalsis and secretomotor functions (i.e., decreased fluid secretion). Parasympathetic nerve fibers generally increase peristalsis, relax involuntary sphincters, and increase secretomotor activities. The extrinsic innervation of the intestines is integrated with the intrinsic (enteric) innervation. Autonomic gastrointestinal neuropathies such as those seen in diabetes most commonly result in constipation, requiring treatment with pharmacological agents and high-fiber agents. However, diabetic diarrhea also is common and may require treatment to slow secretomotor function.



### 9.64 NERVES OF THE SMALL INTESTINE

This figure shows the anatomy of the extrinsic innervation of the small intestine by the splanchnic and vagal nerves and their associated plexuses.

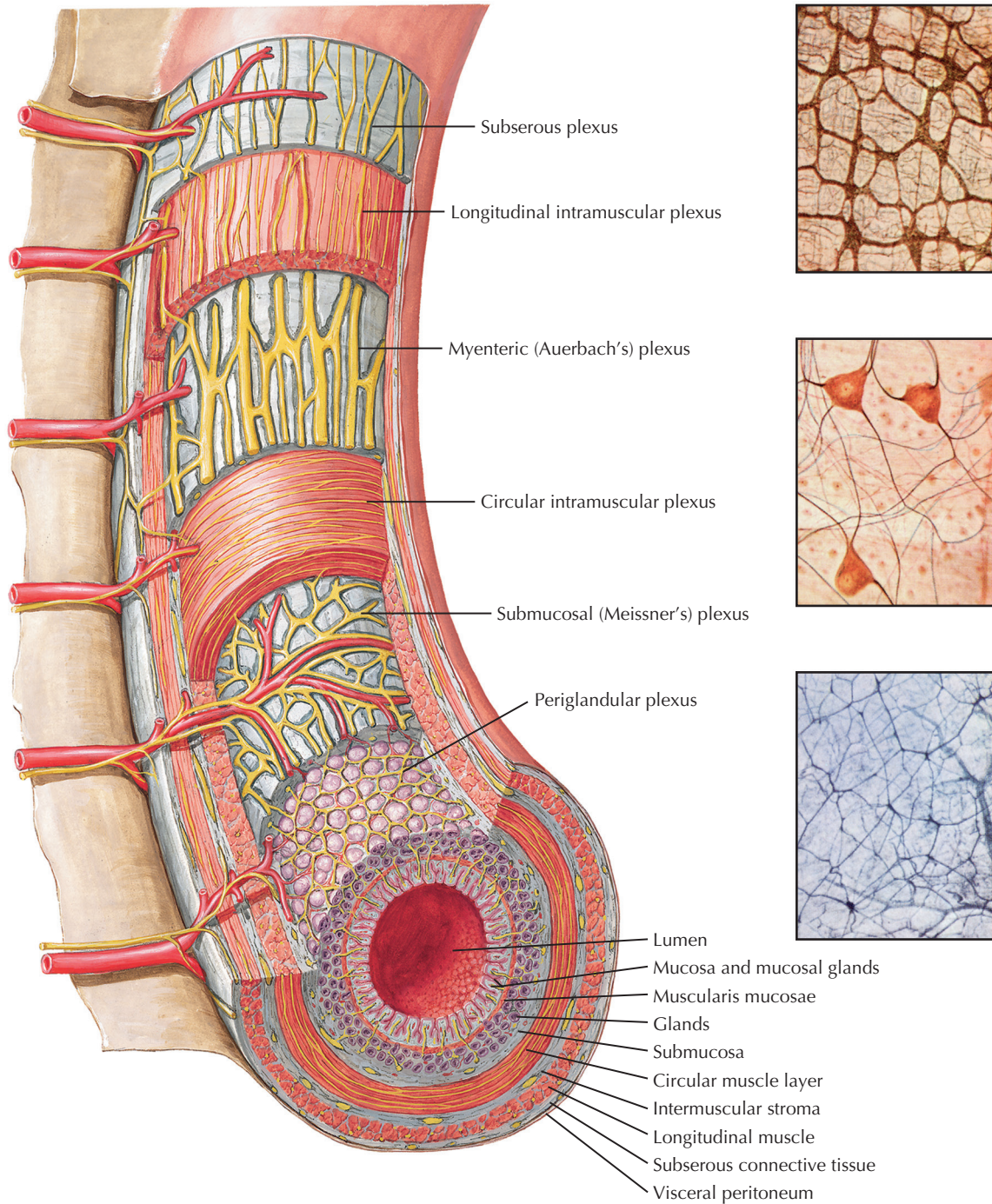




### 9.65 NERVES OF THE LARGE INTESTINE

This figure shows the anatomy of the extrinsic innervation of the large intestine by the splanchnic and vagal nerves and their associated plexuses.





Myenteric plexus lying on longitudinal muscular layer. Fine secondary bundles crossing meshes (duodenum of guinea pig, Champy-Coujard, osmic stain,  $\times 20$ )

Group of multipolar neurons, type II, in ganglion of myenteric plexus (ileum of cat, Bielschowsky, silver stain,  $\times 200$ )

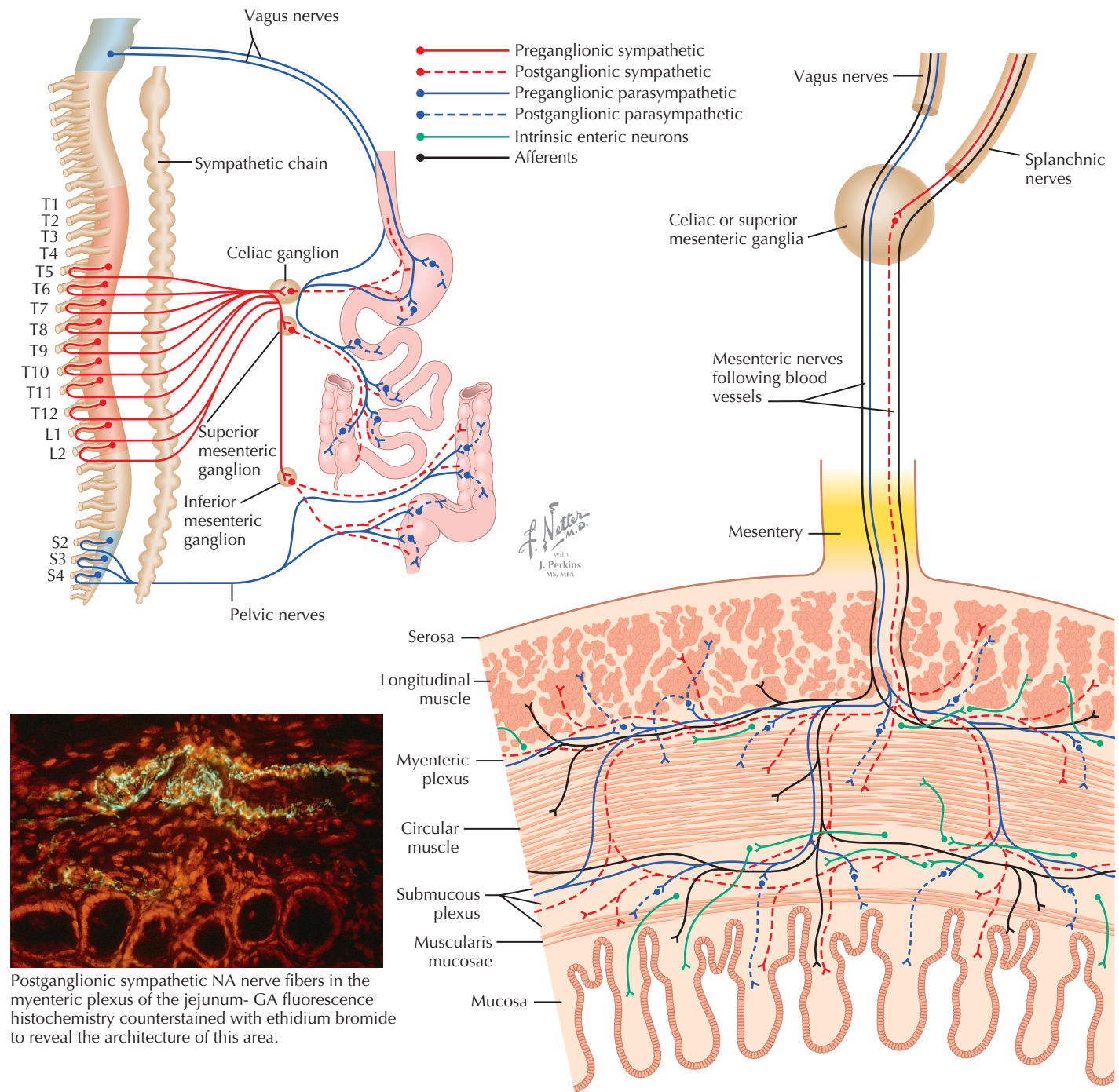
Submucous plexus (ascending colon of guinea pig, stained by Golgi impregnation,  $\times 20$ )

*F. Netter M.D.*

### 9.66 ENTERIC NERVOUS SYSTEM: LONGITUDINAL VIEW

The enteric nervous system is made up of approximately 100 million neurons arranged principally in submucosal (Meissner's) and myenteric (Auerbach's) plexuses; it provides intrinsic innervation to the small and large intestines. Neurons of this system interconnect with one another and with neuronal processes of the autonomic nervous system, although most neuronal components of this network are free of autonomic influence. The enteric plexuses regulate peristaltic responses (which can proceed without extrinsic innervation), pacemaker activity, and other automated secretory processes. The

myenteric plexus controls primarily motility; the submucosal plexus controls primarily fluid secretion and absorption. More than 20 distinct neurotransmitters have been identified in enteric neurons (e.g., ACh, substance P, serotonin, VIP, somatostatin, nitric oxide). ACh and substance P are excitatory to smooth muscle, whereas VIP and nitric oxide are inhibitory. Extrinsic autonomic innervation helps to coordinate these enteric plexuses and circuits; optimal functioning of the gastrointestinal tract requires coordinated interactions among endocrine, paracrine, and neurocrine mediators. Disturbance of extrinsic innervation by a neuropathy can result in disorders of motility such as constipation or diarrhea.



Postganglionic sympathetic NA nerve fibers in the myenteric plexus of the jejunum- GA fluorescence histochemistry counterstained with ethidium bromide to reveal the architecture of this area.

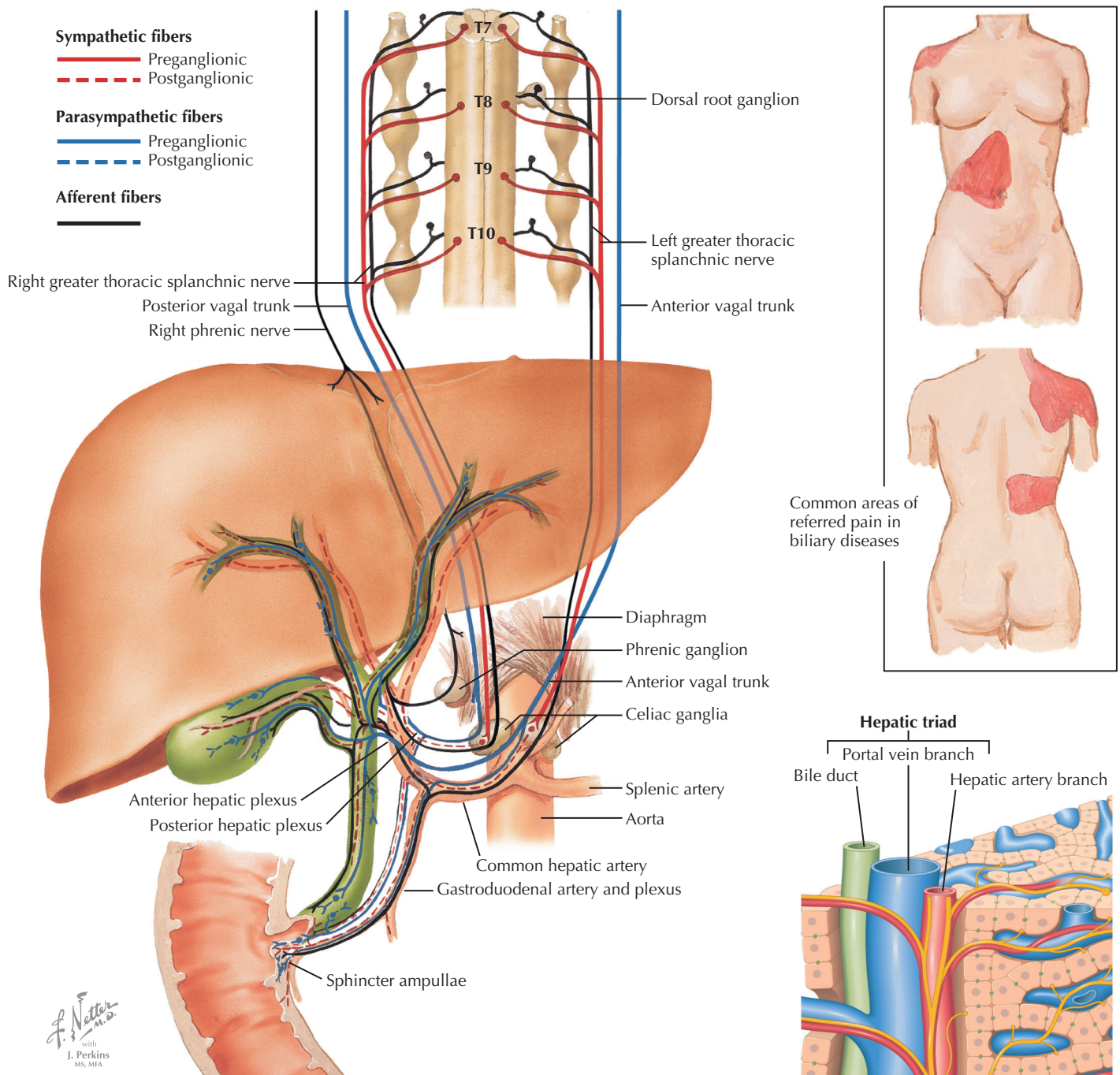
### 9.67 ENTERIC NERVOUS SYSTEM: CROSS-SECTIONAL VIEW

In the myenteric and the submucosal plexuses, some neurons are innervated by sympathetic nerve fibers from the sympathetic chain and collateral ganglia and by vagal or pelvic splanchnic parasympathetic nerve fibers; other neurons are independent of autonomic regulation. Autonomic postganglionic nerve fibers and intrinsic neuropeptidergic nerve fibers also supply macrophages, T lymphocytes, plasma cells, and other cells of the immune system with innervation. This provides a regulatory network that modulates the host defenses of the gastrointestinal tract and the immune reactivity of gut-associated lymphoid tissue.

#### CLINICAL POINT

The intrinsic neuronal clusters that form the enteric nervous system derive from the neural crest. If these neural crest derivatives fail to migrate properly into the colon, as occurs in a developmental abnormality called Hirschsprung's disease (chronic megacolon), the intrinsic circuitry for peristalsis, pacemaker activity, and other gut functions cannot occur. The vagus nerve and sympathetic innervation from the pelvic splanchnic nerves cannot coordinate the activity of the colon in the absence of its enteric components. Therefore, megacolon (intestinal obstruction) results from absent peristalsis and loss of smooth muscle tone of the colon. Distention and hypertrophy of the colon may ensue.





### 9.68 AUTONOMIC INNERVATION OF THE LIVER AND BILIARY TRACT

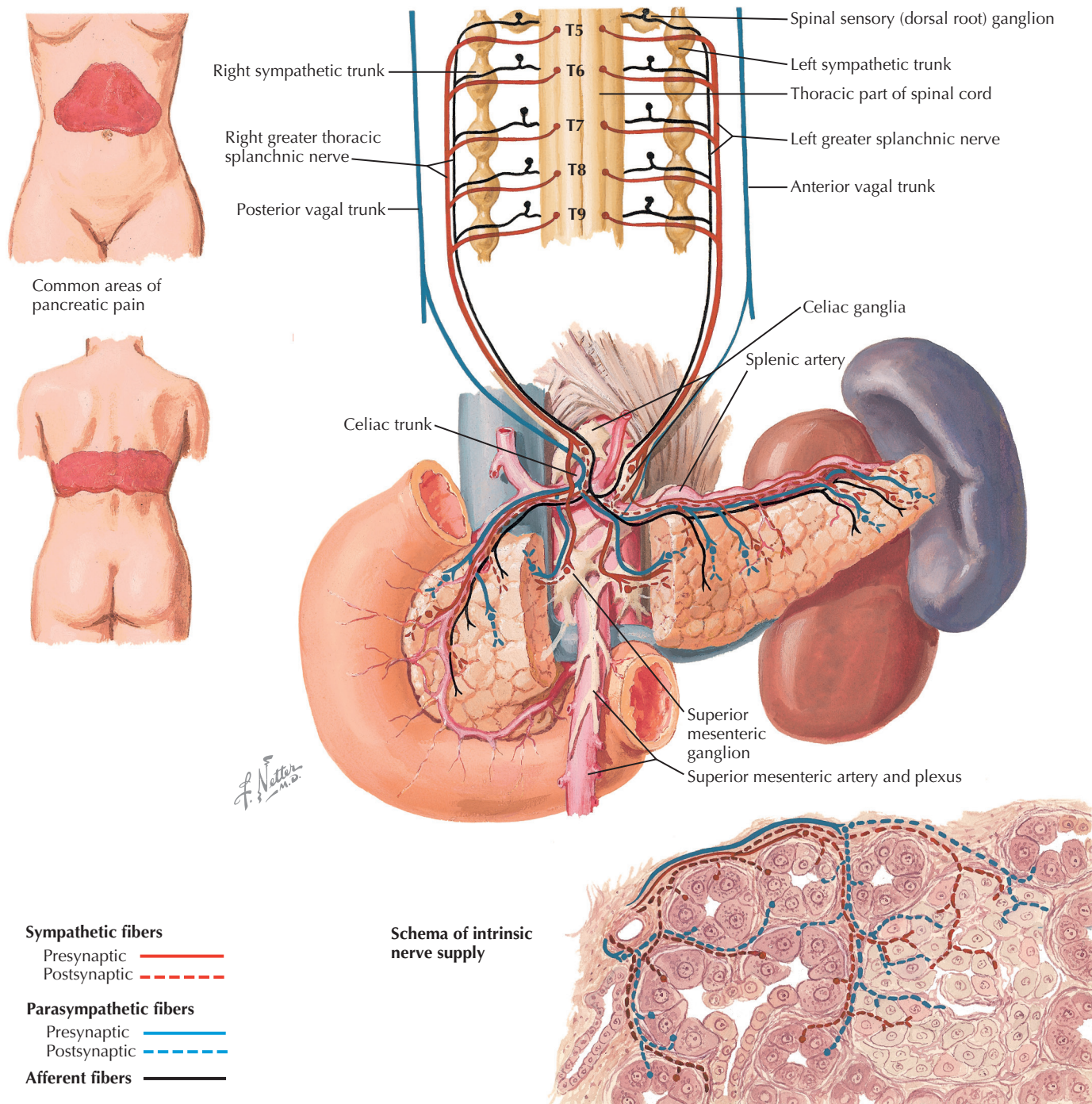
Sympathetic nerve fibers to the liver derive from T7–T10 of the spinal cord and distribute mainly via the celiac ganglion and its associated plexus. Parasympathetic nerve fibers to the liver derive from the abdominal vagus nerve. Postganglionic noradrenergic sympathetic nerve fibers end directly adjacent to hepatocytes; norepinephrine released from these nerve fibers initiates glycogenolysis and hyperglycemia for fight-or-flight responses and induces gluconeogenesis. Autonomic innervation helps to regulate vascular, secretory, and phagocytic processes in the liver. The gallbladder, especially the sphincter ampullae and the sphincter of the choledochal duct, is also supplied by autonomic nerve fibers. The sympathetic nerve fibers cause contraction of the sphincters and dilation of the gallbladder; the parasympathetic nerve fibers

cause opening of the sphincters and contraction of the gallbladder.

#### CLINICAL POINT

Postganglionic sympathetic noradrenergic nerves to the liver can trigger glycogenolysis and gluconeogenesis, providing glucose as fuel for sympathetic arousal. Chronic activation of the SNS, with increased secretion of norepinephrine, can drive glucose levels, provoke insulin secretion, increase free-radical formation, increase platelet aggregation, and initiate other actions that are beneficial in an emergency but problematic when present chronically. These connections may be one route by which chronic stressors intersect with metabolic syndrome, diminish antiviral and antitumor immunity, and increase the risk for a variety of chronic diseases, including hypertension, cardiovascular disease and stroke, some cancers, and type II diabetes. Autonomic neuropathy to the gallbladder can result in atonic smooth muscle responses, with the development of gallstones (especially in individuals with hypercholesterolemia) and diarrhea.

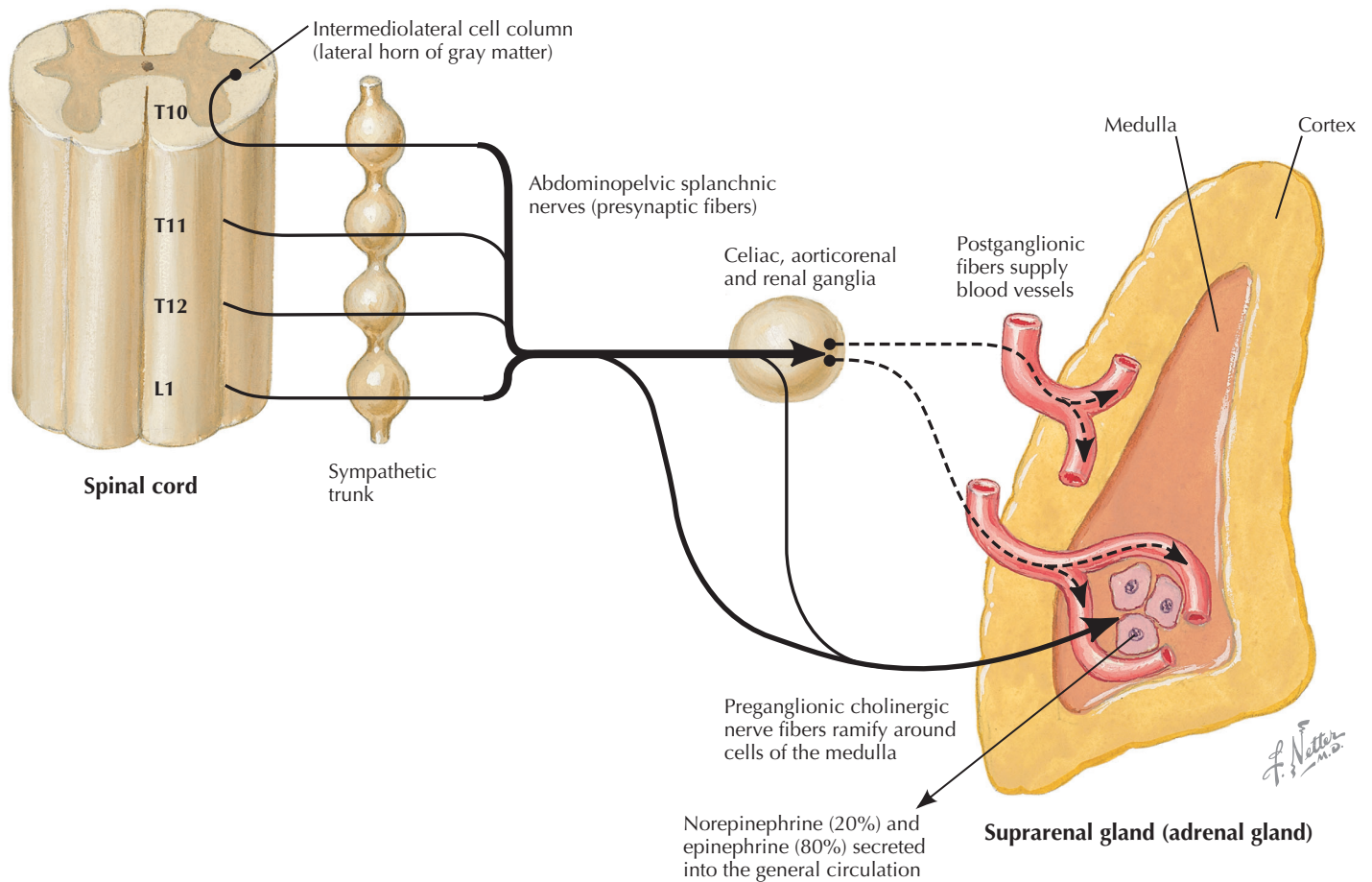




### 9.69 AUTONOMIC INNERVATION OF THE PANCREAS

Secretion by the pancreas is under both neural and endocrine control. Pancreatic exocrine glands and endocrine cells (islets of Langerhans) are innervated by parasympathetic subdiaphragmatic vagal nerve fibers via intramural ganglia and by sympathetic nerve fibers derived from T5–T9 intermediolateral spinal cord gray via the celiac ganglion. Although only a small anatomical component of the pancreas (1%), the endocrine pancreas secretes several vital endocrine products, including glucagon (a fuel-mobilizing hormone); insulin (a fuel-storing hormone); somatostatin (a suppressor of glucagon and insulin secretion); and pancreatic polypeptide (an inhibitor of the secretion of enzymes and  $\text{HCO}_3^-$ , the bicarbonate ion, by the exocrine pancreas). ACh supplied by the parasympathetic fibers stimulates insulin secretion by islet cells, and norepinephrine secretion by the sympathetic fibers (as well as epinephrine by the adrenal medulla) inhibits insulin secretion from the islet cells. ACh stimulates a variety of hormones. Secretin acts on ductal cells of the pancreas to stimulate secretion of fluid with a high  $\text{HCO}_3^-$  content. Cholecystikinin is secreted by I cells in response to fats in the duodenum and upper jejunum and acts on acinar cells to stimulate the secretion of enzymes.

gones and insulin secretion); and pancreatic polypeptide (an inhibitor of the secretion of enzymes and  $\text{HCO}_3^-$ , the bicarbonate ion, by the exocrine pancreas). ACh supplied by the parasympathetic fibers stimulates insulin secretion by islet cells, and norepinephrine secretion by the sympathetic fibers (as well as epinephrine by the adrenal medulla) inhibits insulin secretion from the islet cells. ACh stimulates a variety of hormones. Secretin acts on ductal cells of the pancreas to stimulate secretion of fluid with a high  $\text{HCO}_3^-$  content. Cholecystikinin is secreted by I cells in response to fats in the duodenum and upper jejunum and acts on acinar cells to stimulate the secretion of enzymes.

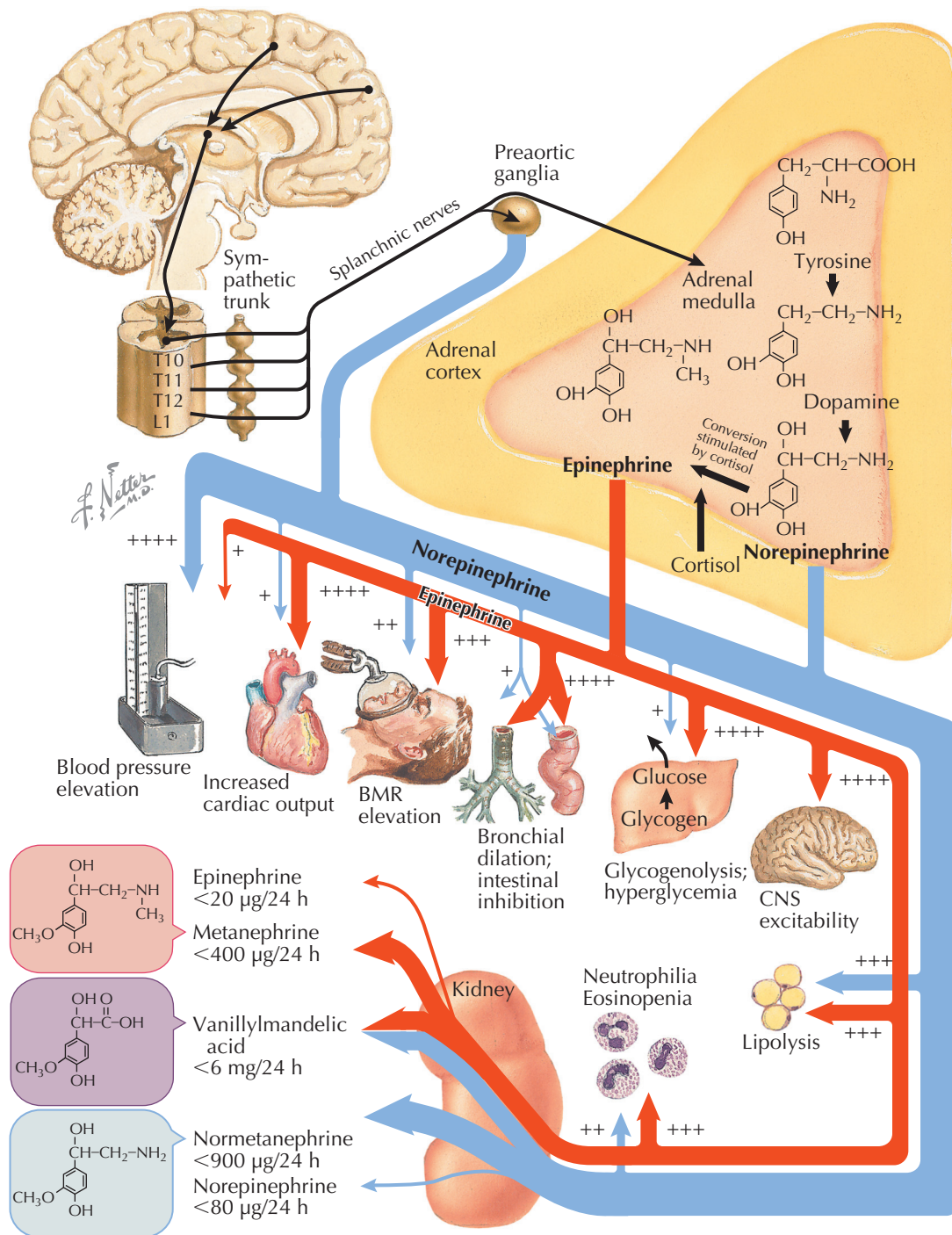


### 9.70 SCHEMATIC OF INNERVATION OF THE ADRENAL GLAND

Sympathetic preganglionic nerve fibers from neurons in the T10–L1 intermediolateral cell column pass through the sym-

pathetic chain, travel in splanchnic nerves, and directly innervate adrenal medullary chromaffin cells. These chromaffin cells are of neural crest origin and function as sympathetic ganglion cells.



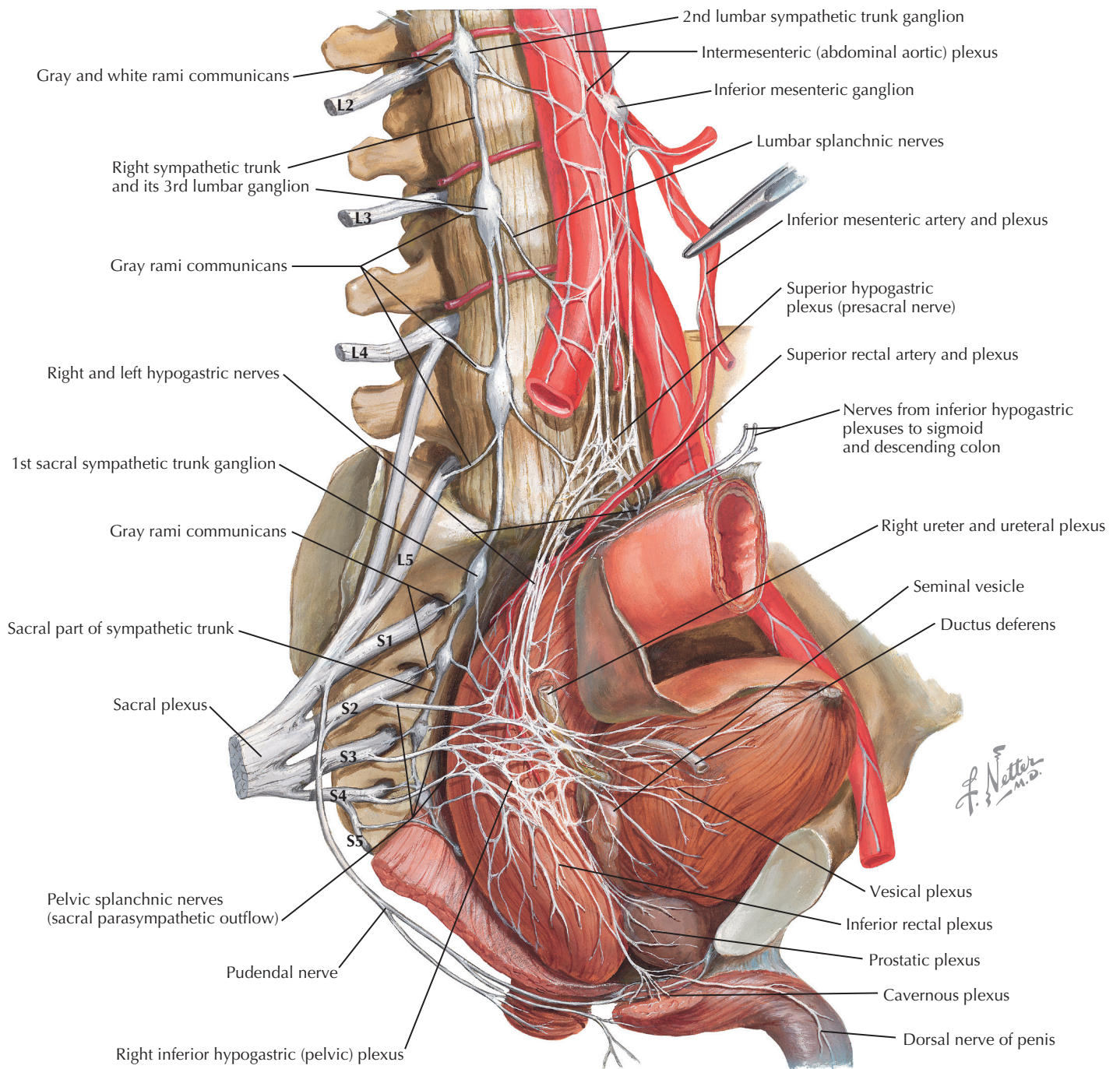


### 9.71 INNERVATION OF THE ADRENAL GLAND

The adrenal medullary chromaffin cells act as modified sympathetic ganglion cells, which are innervated by preganglionic sympathetic nerve fibers from T10 to L1 intermediolateral cells of the spinal cord. An adrenal portal system conveys blood directly from the adrenal cortex to the adrenal medulla. Cortisol, derived from action of the hypothalamo-pituitary-adrenal axis, bathes the chromaffin cells in very high concentrations, inducing the enzyme phenylethanolamine-*N*-methyl-transferase, which is responsible for the synthesis of epinephrine. Approximately 70% to 80% of the adrenal medullary output of catecholamines is epinephrine; the remaining

output is norepinephrine. Both epinephrine and norepinephrine can be taken up into sympathetic postganglionic noradrenergic nerve terminals at any site throughout the body by the high-affinity uptake carrier and can be subsequently released. A sympathetic arousal response that generates the secretion of epinephrine from the adrenal medulla will therefore provide altered catecholamine content (higher epinephrine) because of high-affinity uptake in nerve terminals throughout the body; subsequent release of this epinephrine modifies the usual sympathetic balance of alpha versus beta receptor stimulation on target organs for a brief period.





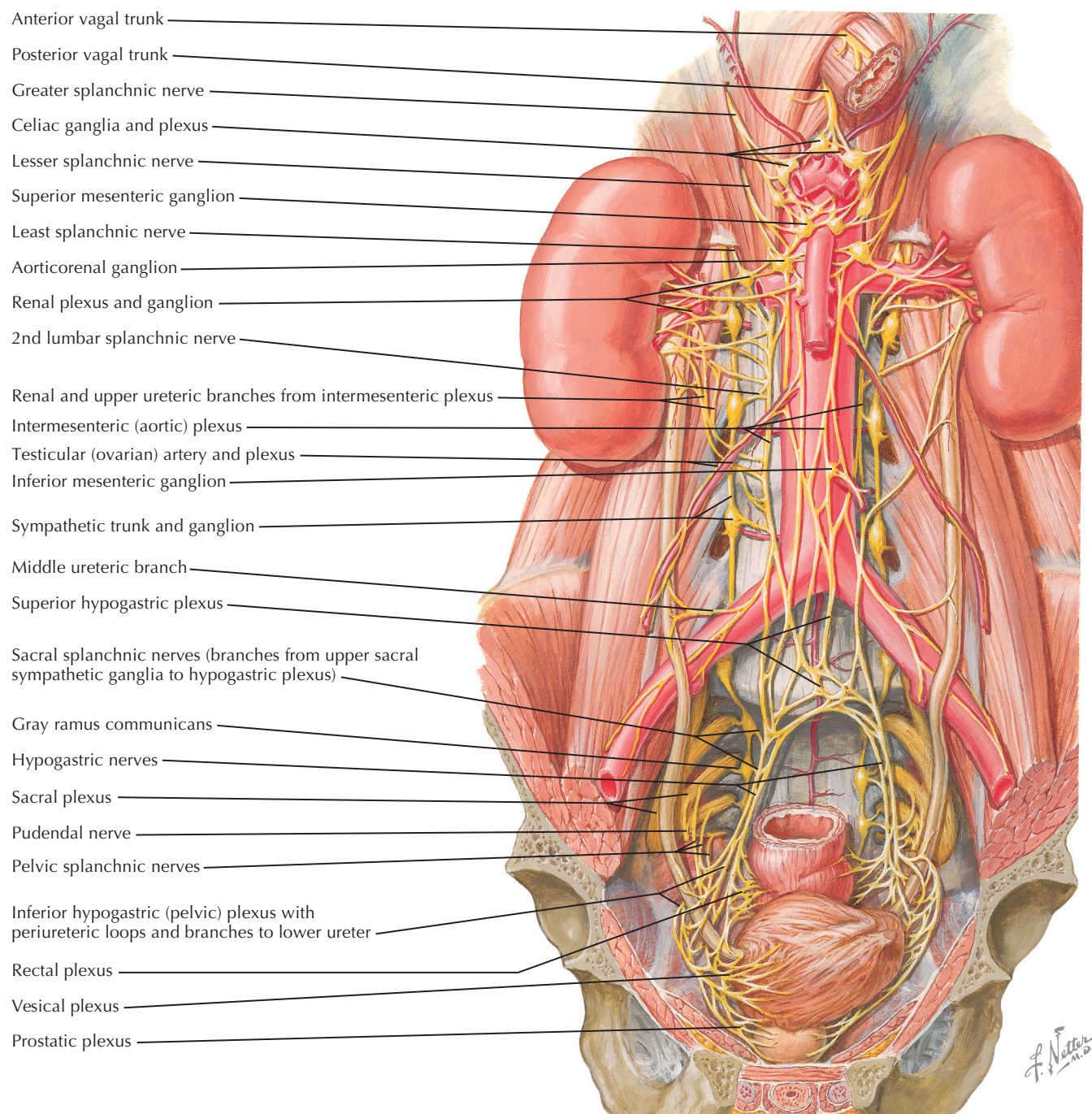
### 9.72 AUTONOMIC PELVIC NERVES AND GANGLIA

Sympathetic nerve fibers supply the pelvis through the sympathetic trunk ganglia and the superior hypogastric plexus. These fibers travel along visceral and vascular nerves to the colon, ureters, and great vessels, such as the inferior mesenteric and common iliac vessels. Parasympathetic nerve fibers arise from the S2–S4 intermediate gray of the spinal cord and travel via the pelvic splanchnic nerves to distribute with the branches of the inferior hypogastric plexus. The parasympathetic ganglia are intramural, in or adjacent to the wall of the organ innervated.

#### CLINICAL POINT

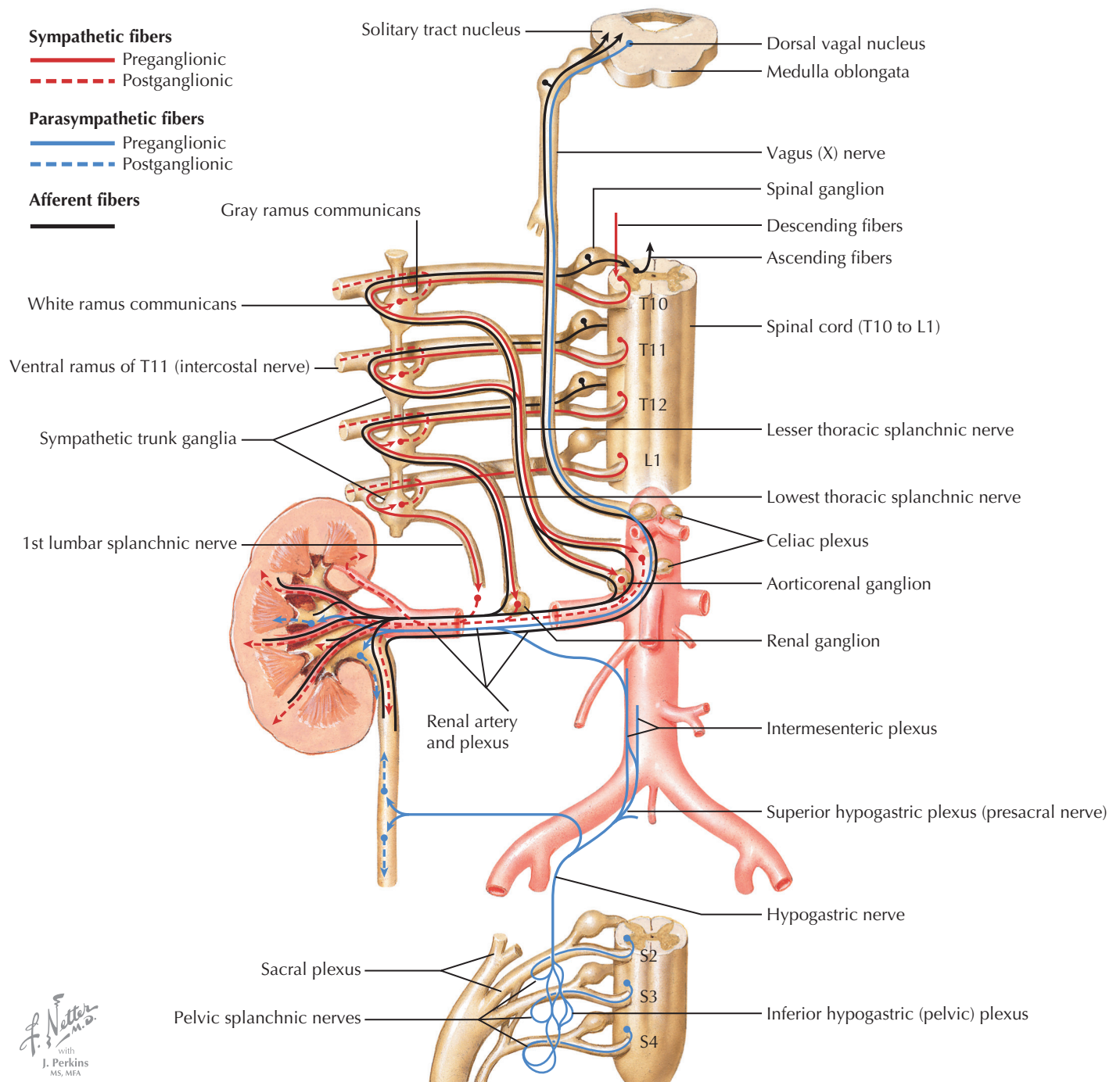
The pelvic nerves and ganglia contain both sympathetic and parasympathetic components. The sympathetic trunk ganglia and superior hypogastric plexus distribute sympathetic nerve fibers to pelvic viscera, and S2–S4 intermediate gray neurons send pelvic splanchnic nerves via the inferior hypogastric plexuses to end in intramural ganglia that supply the pelvic viscera. Of particular functional importance is the autonomic distribution to the bladder and reproductive organs. Lesions in these pelvic autonomic nerves can occur with diabetes, demyelinating diseases, and mass lesions. Damage to pelvic parasympathetic nerves can produce a flaccid bladder with overflow incontinence and can cause erectile impotence in males. It should be noted that both parasympathetic and sympathetic autonomic nerves play roles in sexual function. Parasympathetic nerves are essential for proper erectile function, and sympathetic nerves play a role in ejaculation and may also contribute to erectile function; beta-adrenergic blockers sometimes have the side effect of erectile dysfunction.





### 9.73 NERVES OF THE KIDNEYS, URETERS, AND URINARY BLADDER

This schematic demonstrates the nerves that distribute to the kidneys, ureters, and urinary bladder.

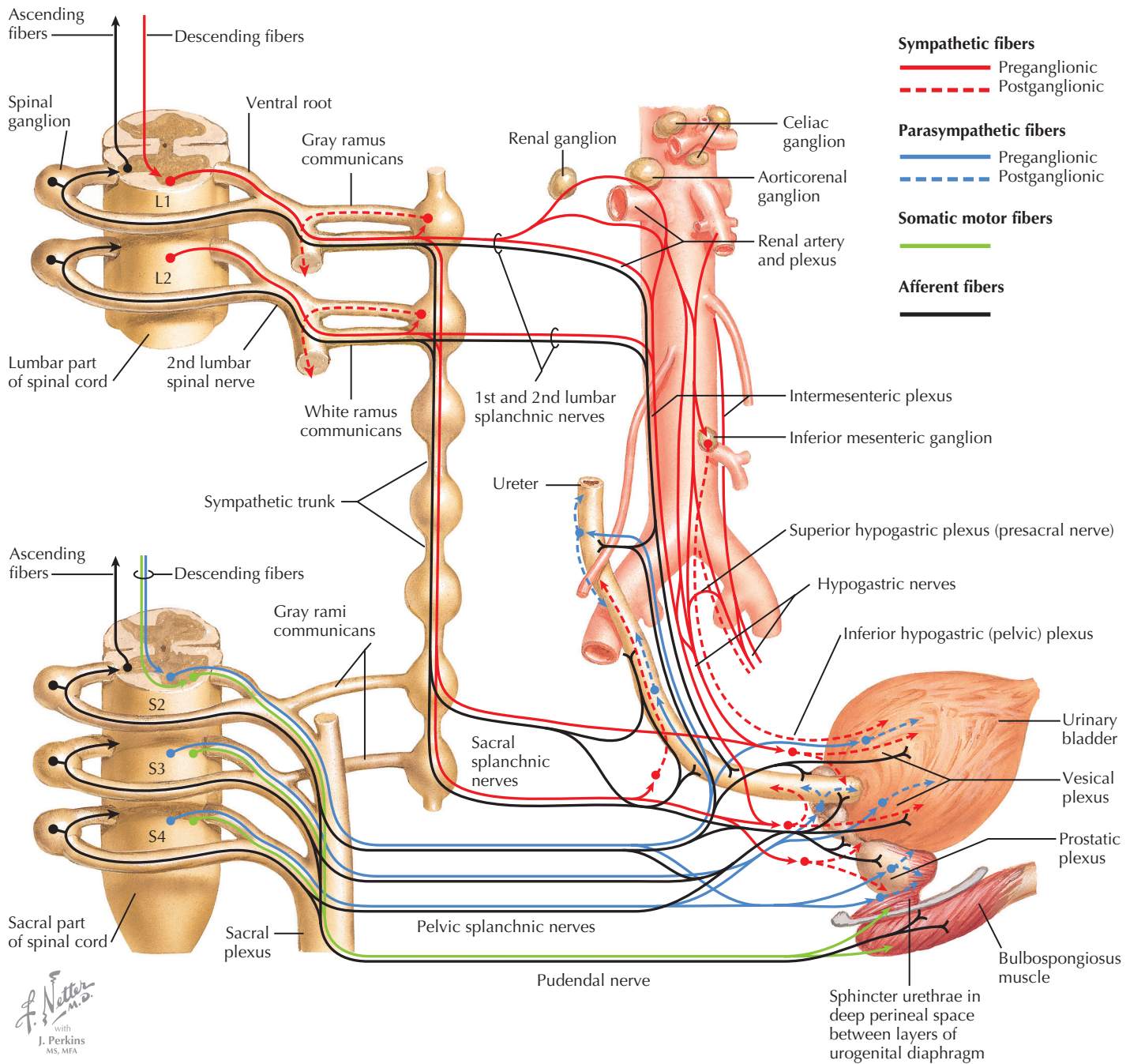


### 9.74 INNERVATION OF THE KIDNEYS AND UPPER URETER

Sympathetic innervation of the kidneys and upper ureter arises from the T10–L1 intermediolateral cell column preganglionic neurons in the spinal cord and travels through lower thoracic and upper lumbar splanchnic nerves to synapse in the celiac or aorticorenal ganglia. Noradrenergic postganglionic fibers travel in fascicles that accompany the upper ureteric, renal, pelvic, calyceal, and segmental branches of the renal vessels. Parasympathetic nerve fibers are distributed to renal ganglia by the vagus nerve and pelvic splanchnic

nerves via a longer course through other plexuses. The sympathetic nerve fibers stimulate renin secretion (and the renin-angiotensin-aldosterone system); decrease the glomerular filtration rate; stimulate proximal tubule and collecting duct sodium chloride reabsorption (further elevating blood pressure); and stimulate contraction of the ureters. Parasympathetic nerve fibers cause relaxation of smooth muscle in the pelvis, the calyces, and the upper ureter and, when accompanied by decreased sympathetic activation, may lead to a decrease in blood pressure.





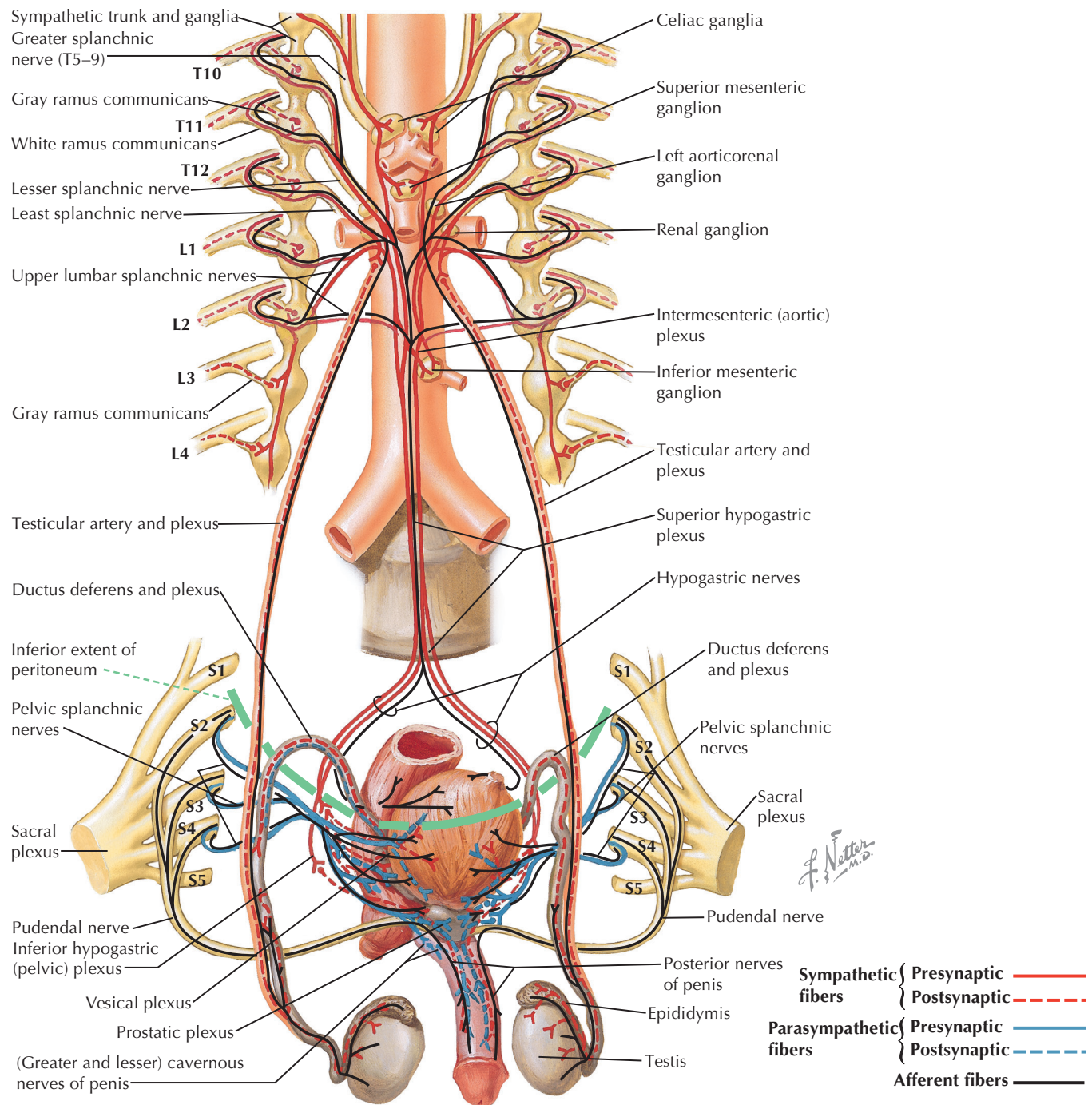
### 9.75 INNERVATION OF THE URINARY BLADDER AND LOWER URETER

The sympathetic innervation of the bladder and lower ureter derives mainly from the L1–L2 preganglionic neurons in the spinal cord and travels through sacral splanchnic nerves to the hypogastric plexus. Parasympathetic innervation derives from the S2–S4 intermediate gray of the spinal cord and distributes to intramural ganglia in the wall of the bladder via pelvic splanchnic nerves. Sympathetic nerve fibers relax the detrusor muscle and contract the trigone and the internal sphincter. Parasympathetic nerve fibers contract the detrusor muscle and relax the trigone and the internal sphincter, thus stimulating emptying of the bladder. Sensory nerves also are present

in the bladder; when the bladder is stretched because it is full, these nerves can initiate the sensation of the need to empty the bladder.

#### CLINICAL POINT

Parasympathetic nerve damage, particularly in diabetic neuropathy, results in initial problems of incomplete emptying of the bladder, dribbling, and urinary stasis sufficient to increase the likelihood of infection. Later in the course of parasympathetic damage, a flaccid bladder with incomplete emptying and incontinence can occur. Sensory neuropathy also can result in an enlarged bladder caused by incomplete emptying because of the inability of the patient to sense fullness and by the decreased sense of urgency for urination.



### 9.76 INNERVATION OF THE MALE REPRODUCTIVE ORGANS

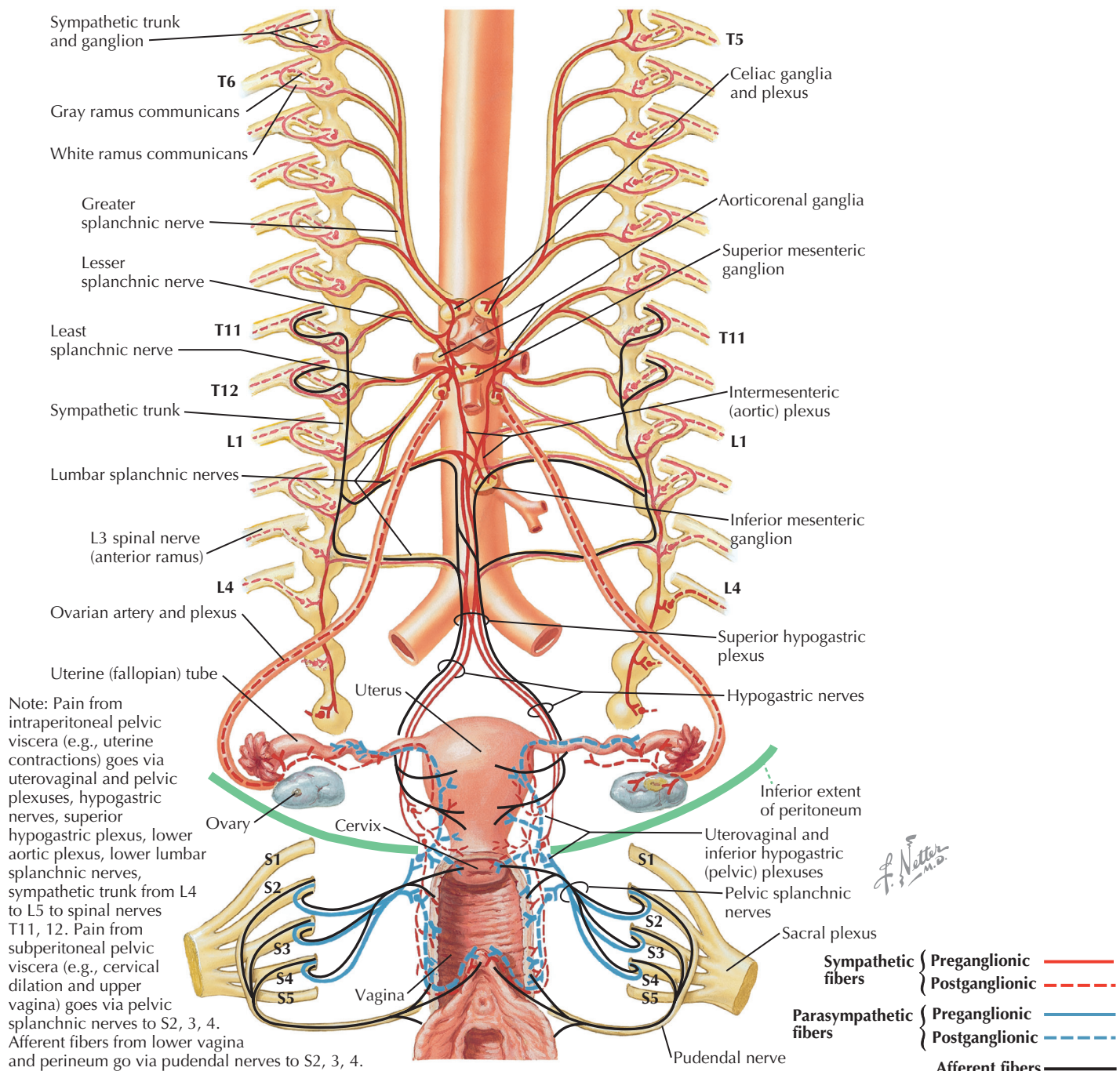
Sympathetic innervation to the male reproductive organs derives from T10–L2 intermediolateral cell column neurons and reaches the hypogastric plexus via thoracic and upper lumbar splanchnic nerves. Parasympathetic innervation derives from the S2–S4 intermediate gray of the spinal cord and travels to the inferior hypogastric plexus via pelvic splanchnic nerves. Sympathetic nerve fibers cause contraction of the vas deferens and prostatic capsule and contract the sphincter to the bladder, which prevents retrograde ejaculation. Sympathetic nerve fibers also contribute to vascular responses in the penile corpora cavernosa that are related to erection; beta-receptor blockade can result in erectile dysfunction. Parasympathetic nerve fibers regulate the vascular dila-

tion that initiates and maintains penile erection. Sympathetic and parasympathetic nerve fibers must work together to optimize sexual and reproductive function.

#### CLINICAL POINT

Parasympathetic nerve damage may lead to autonomic erectile dysfunction. Some individuals taking beta blockers might have similar responses. However, erectile function also depends extensively on psychological, perceptive, and sensory factors in addition to the need for coordinated autonomic function. Pharmacological compounds that enhance erectile function influence vascular responses through the production of nitric oxide to promote erection; these drugs may interact adversely with alpha-blockers used to treat benign prostatic hyperplasia and other conditions, resulting in hypotensive responses that are potentially fatal.





### 9.77 INNERVATION OF THE FEMALE REPRODUCTIVE ORGANS

Autonomic nerves supplying the female reproductive organs have origins similar to those supplying their male counterparts. Sympathetic nerves can stimulate contraction of the uterus, but the extent of this action is determined also by hormonal receptor responsiveness and neurotransmitter receptor expression. Sympathetic nerve fibers also supply the

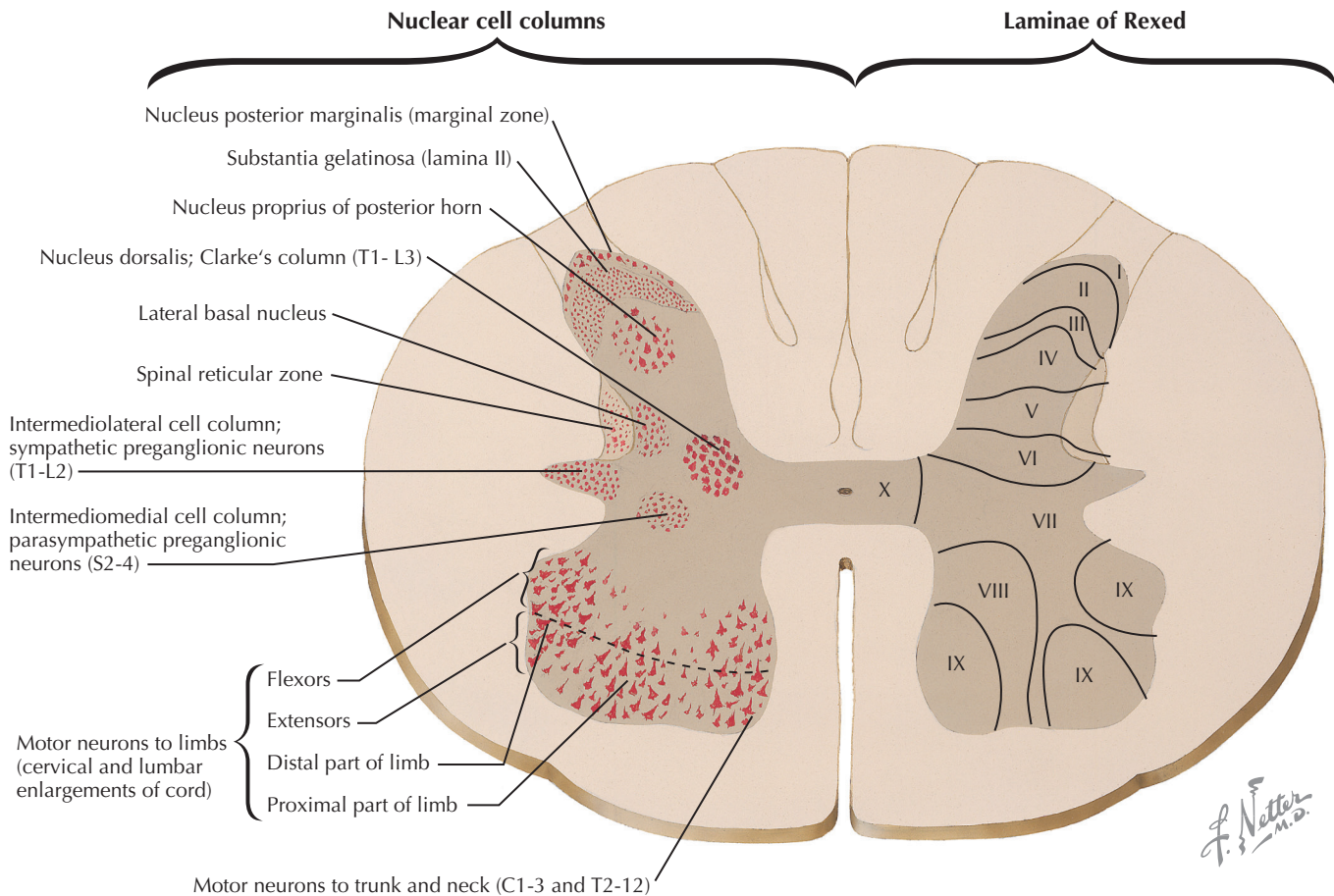
vaginal arteries, the vestibular glands, and erectile tissue. Parasympathetic nerve fibers supply the muscular and mucous coats of the vagina and urethra, stimulate the erectile tissue of the vestibular bulb and corpora cavernosa of the clitoris, and supply the vestibular glands. Autonomic neuropathy affecting the nerves to female reproductive organs may result in dry, atrophic vaginal walls with very little lubrication, resulting in dyspareunia (painful intercourse).



# 10

## SPINAL CORD

- 10.1 Cytoarchitecture of the Spinal Cord Gray Matter
- 10.2 Spinal Cord Levels: Cervical, Thoracic, Lumbar, and Sacral
- 10.3 Spinal Cord Levels: Cervical, Thoracic, Lumbar, and Sacral (Continued)
- 10.4 Spinal Cord Levels: Cervical, Thoracic, Lumbar, and Sacral (Continued)
- 10.5 Spinal Cord Levels: Cervical, Thoracic, Lumbar, and Sacral (Continued)
- 10.6 Spinal Cord Histological: Cross Sections
- 10.7 Spinal Cord Histological: Cross Sections (Continued)
- 10.8 Spinal Cord Imaging
- 10.9 Spinal Cord Syndromes
- 10.10 Spinal Cord Lower Motor Neuron Organization and Control
- 10.11 Spinal Somatic Reflex Pathways
- 10.12 Muscle and Joint Receptors and Muscle Spindles
- 10.13 The Muscle Stretch Reflex and Its Central Control via Gamma Motor Neurons

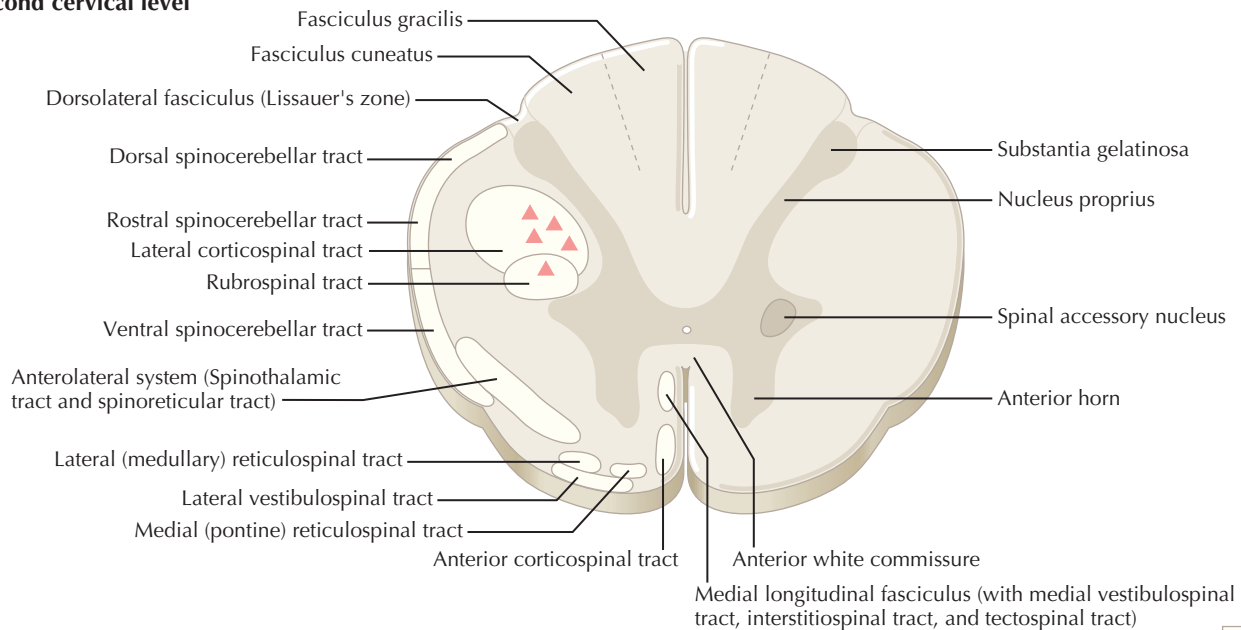
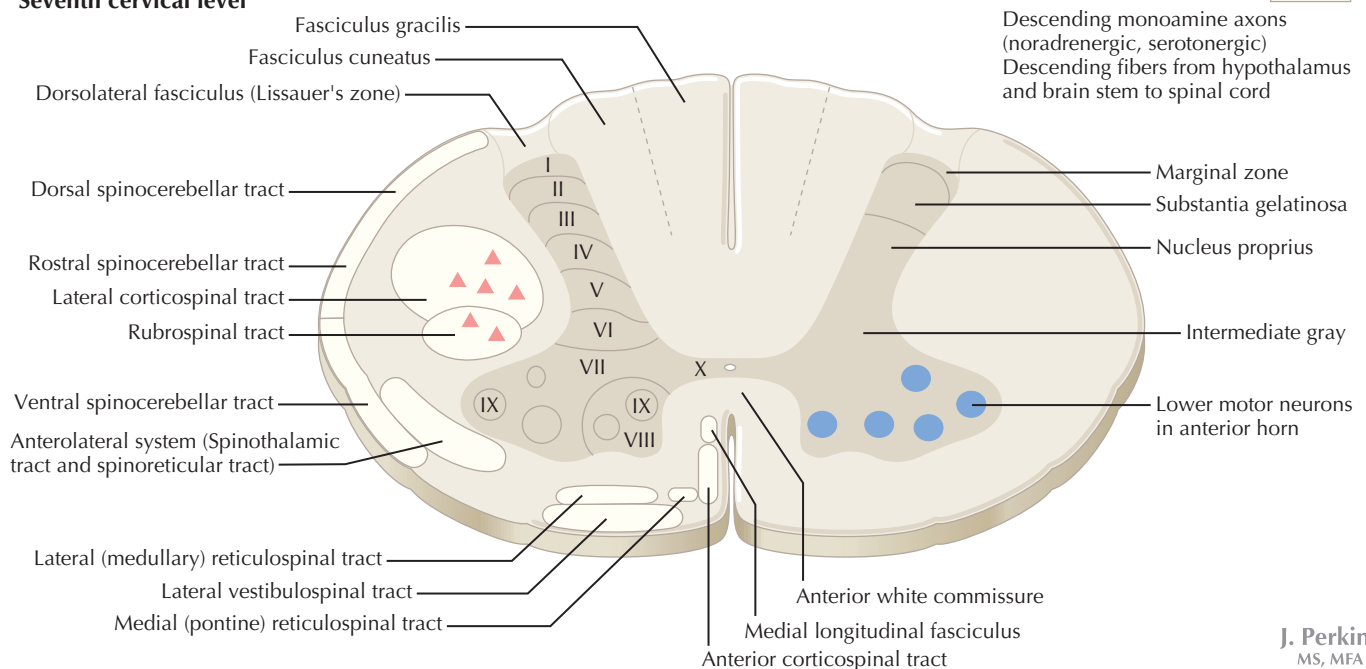


## 10.1 CYTOARCHITECTURE OF THE SPINAL CORD GRAY MATTER

The spinal cord gray matter is located centrally in the interior of the spinal cord in a butterfly pattern. The gray matter is subdivided into three horns: (1) the dorsal horn, a site of major sensory processing; (2) the intermediate gray with a lateral horn, a site where preganglionic sympathetic (thoracolumbar) and parasympathetic (sacral) neurons reside and where interneuronal processing occurs; and (3) the ventral horn, a site where lower motor neurons (LMNs) reside and where converging reflex and descending control of LMNs occurs. Neuronal cell groups appear homogeneous in some regions of gray matter, intermixed with a presence of some discrete nuclei (e.g., Clarke's nucleus, substantia gelatinosa). Laminae of Rexed, an alternative system of cytoarchitectural classification established in the 1950s, subdivides the spinal cord gray matter into ten laminae. This system is used extensively for the dorsal horn and the intermediate gray, laminae I–VII, particularly in conjunction with anatomical details of nociceptive processing and for some reflex and cerebellar processing. Although these laminae have distinctive characteristics at each segmental level, they show some similarities across segmental levels. The absolute amount of spinal cord gray is more extensive in the cervical and lumbosacral enlargements of the spinal cord, which correspond to zones associated with limb innervation, than it is in upper cervical, thoracic, and sacral regions.

### CLINICAL POINT

Classical descriptions of secondary sensory processing in the spinal cord describe neurons of lamina I (marginal zone) and lamina V of the dorsal horn as cells of origin for crossed projections into the spinothalamic/anterolateral system for the processing of pain and temperature sensation (protopathic modalities). Primary sensory large-diameter axons, carrying information about fine discriminative touch, vibratory sensation, and joint position sense (epicritic modalities), enter through the dorsal root entry zone and travel rostrally into the dorsal column system, bypassing synapses in the spinal cord; these axons terminate in their secondary sensory nuclei, gracilis and cuneatus, in the caudal medulla. According to this scheme, pure dorsal column lesions should result in the total loss of epicritic sensation on the ipsilateral side of the body below the level of the lesion. However, such lesions result in diminution of these epicritic sensations or in the inability to discriminate vibratory sensations of different frequencies, but not in the total loss of these modalities. Only with additional damage to the dorsolateral part of the lateral funiculus is profound loss of epicritic sensation observed. This is because additional dorsal horn neurons receive primary sensory input related to epicritic sensation and send ipsilateral projections into the dorsolateral funiculus, providing additional contributions to lemniscal processing of fine discriminative modalities. In addition, some large-diameter primary axons of the epicritic dorsal column system send collaterals into nociceptive processing zones in the spinal cord, where they can alter pain thresholds and dampen nociception. These collaterals are activated by rubbing an area of the body that has just sustained a potentially painful injury and also are a major mechanism of pain control from dorsal column stimulation.

**Second cervical level****Seventh cervical level**

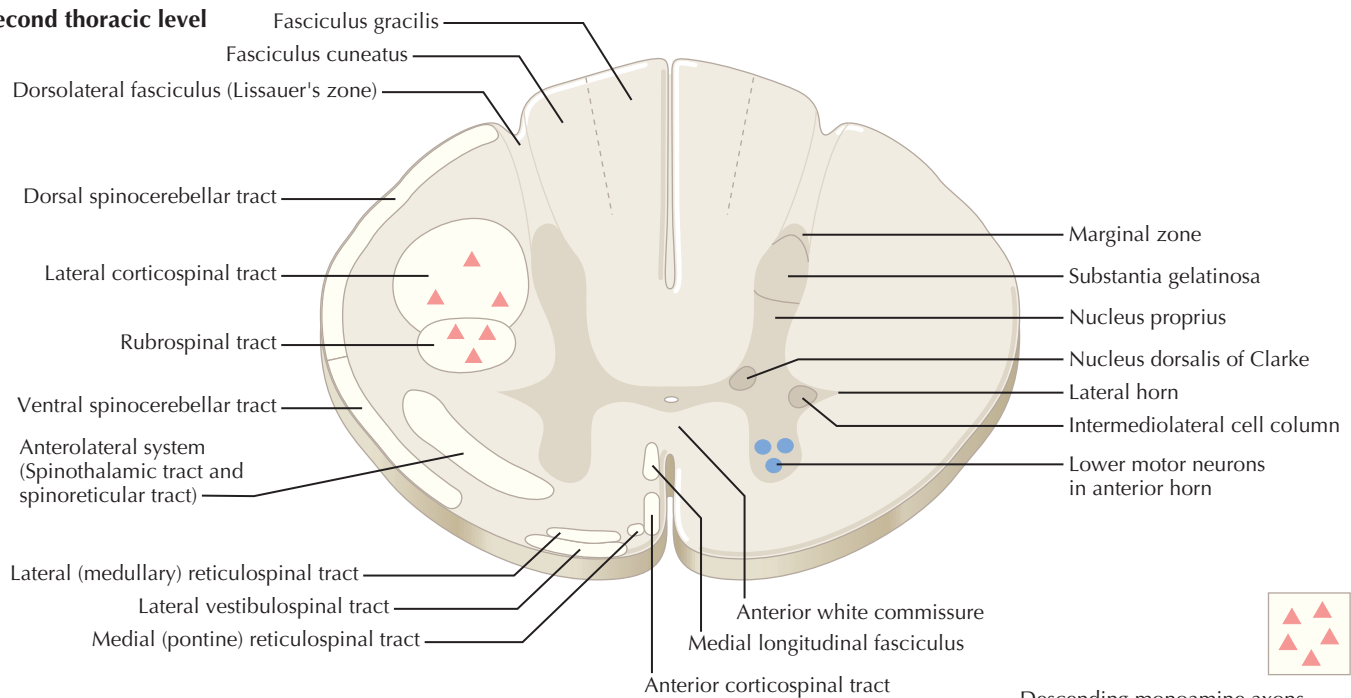
**J. Perkins**  
MS, MFA

## 10.2 SPINAL CORD LEVELS: CERVICAL, THORACIC, LUMBAR, AND SACRAL

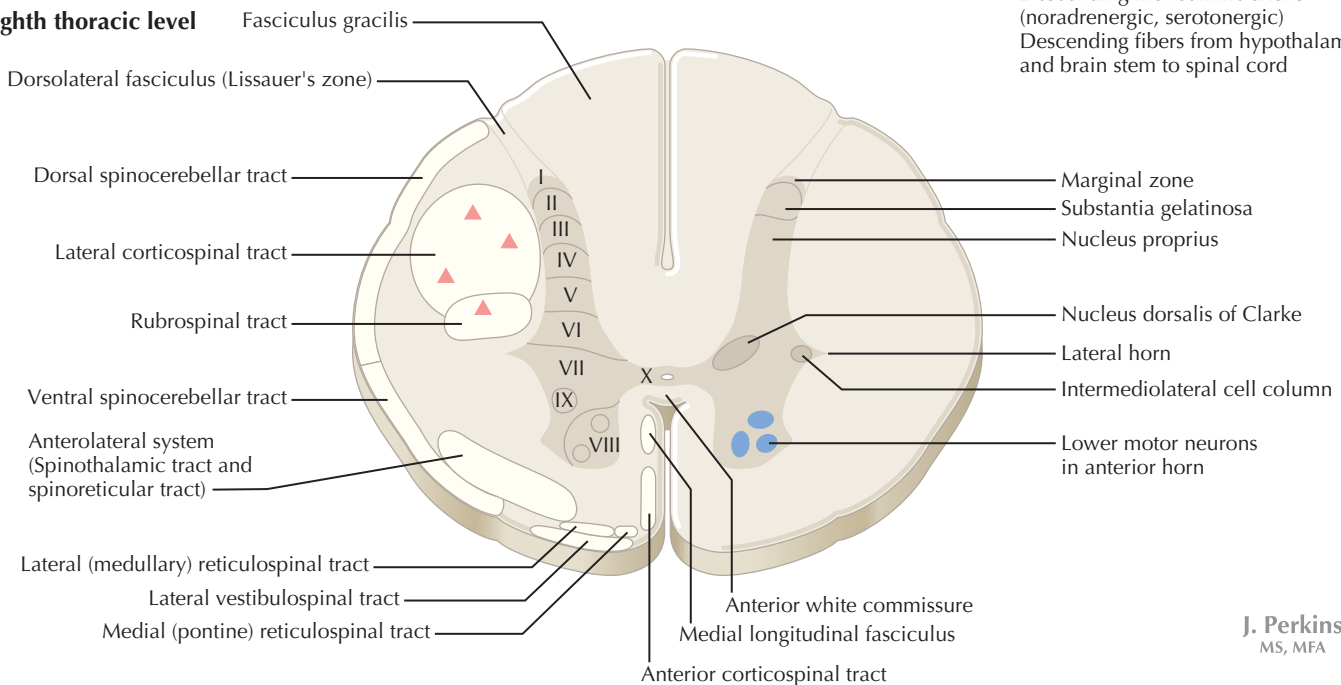
The organization of the gray matter into laminae of Rexed is retained throughout the spinal cord. The dorsal and ventral horns are larger and wider at levels of the cervical and lumbosacral enlargements. The lateral horn is present from L1 to T2. Some nuclei are found only in circumscribed regions, such as the intermediolateral cell column with preganglionic sympathetic neurons (T1–L2 lateral horn); Clarke's nucleus (C8–L2); and the parasympathetic preganglionic nucleus (S2–S4).

The white matter increases in absolute amount from caudal to rostral. The dorsal columns contain only fasciculus gracilis below T6; fasciculus cuneatus is added laterally above T6. The spinothalamic/spinoreticular anterolateral system increases from caudal to rostral. The descending upper motor neuron (UMN) pathways diminish from rostral to caudal. The lateral corticospinal pathway loses more than half of its axons as they synapse in the cervical segments; this tract then diminishes in size as it extends caudally.



**Second thoracic level**

Descending monoamine axons  
(noradrenergic, serotonergic)  
Descending fibers from hypothalamus  
and brain stem to spinal cord

**Eighth thoracic level**

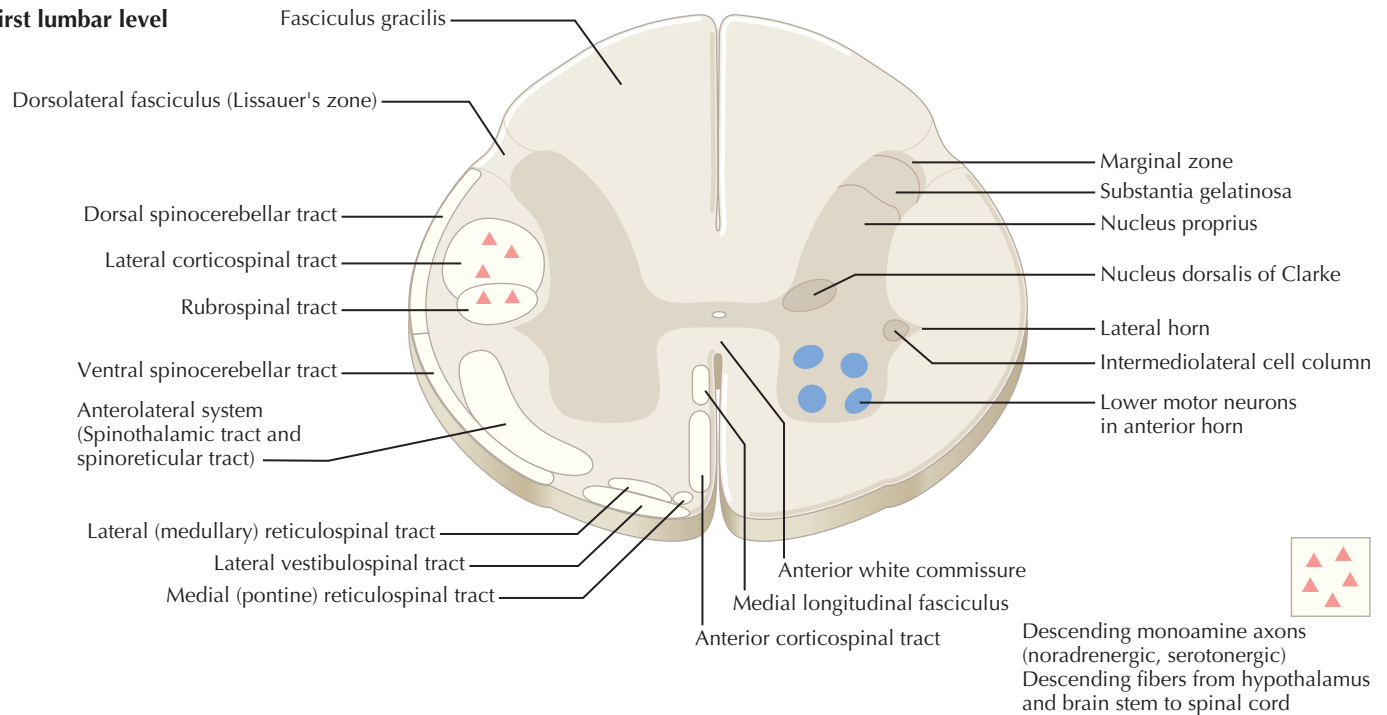
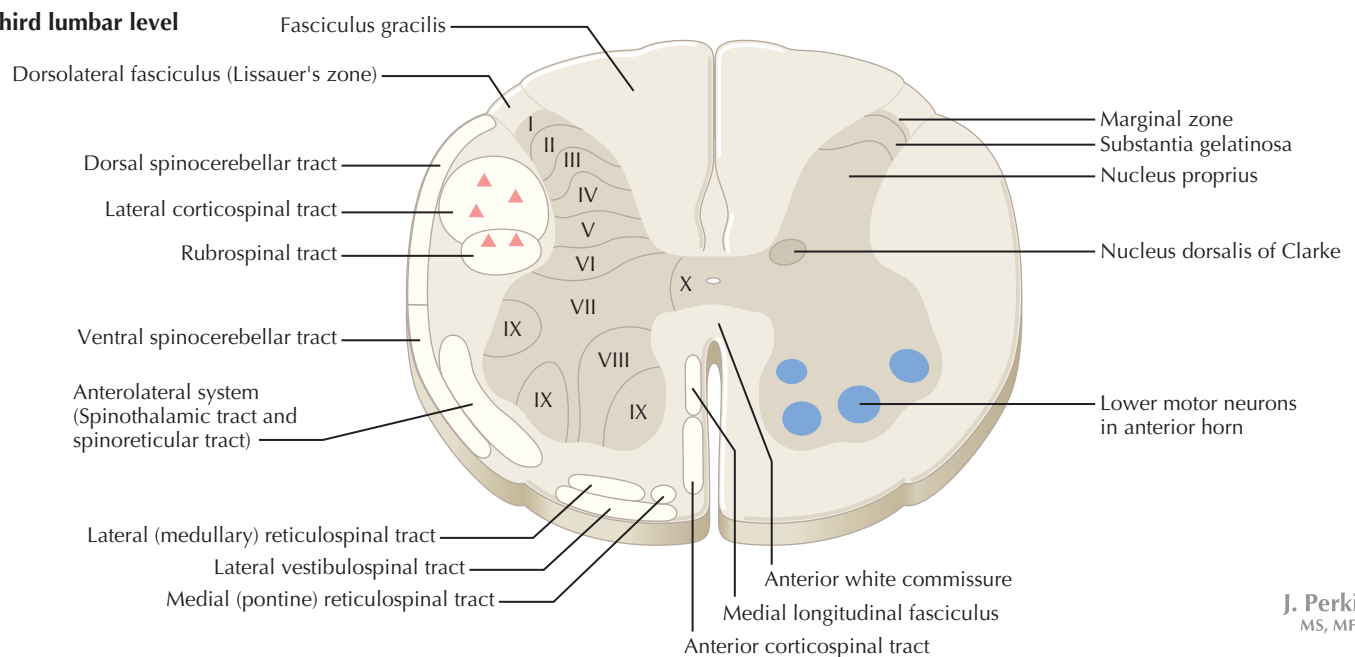
**J. Perkins**  
MS, MFA

### 10.3 SPINAL CORD LEVELS: CERVICAL, THORACIC, LUMBAR, AND SACRAL (continued)

#### CLINICAL POINT

Damage to the lateral funiculus of the cervical spinal cord caused by demyelination, trauma, ischemia, or other causes can lead to disruption of (1) the descending lateral corticospinal tract and rubrospinal tract, resulting in ipsilateral spastic (long-term result) hemiplegia below the level of the lesion; and (2) the descending axons from the hypothalamus to the preganglionic sympathetic neurons in the intermediolateral cell column at the T1 and T2 segments of the cord. These preganglionic neurons supply the superior cervical ganglion, which provides postganglionic noradrenergic sympathetic innervation to the ipsilateral head. Disruption of these descending axons in the lateral funiculus or at any point distal in the sympathetic pathway can result

in Horner's syndrome, which consists of ipsilateral ptosis (because of effects on the superior tarsal muscle), miosis (because of effects on the pupillary dilator muscle), and anhidrosis (less sweat gland activity). Trauma that damages one entire side of the spinal cord at the cervical level produces the same symptoms (ipsilateral spastic paralysis with brisk reflexes, and ipsilateral Horner's syndrome) and also causes (1) flaccid paralysis of ipsilateral muscles innervated by LMNs damaged by the trauma; (2) loss of epicritic sensation (fine discriminative touch, vibratory sensation, joint position sense) ipsilaterally below the level of the trauma because of damage to the dorsal column and dorsolateral funiculus axons; and (3) loss of pain and temperature sensation contralaterally below the level of the lesion because of damage to the anterolateral system (spinothalamic/spinoreticular system). This collection of neurological deficits resulting from a hemisection lesion to the spinal cord is called a Brown-Séquard lesion.

**First lumbar level****Third lumbar level**

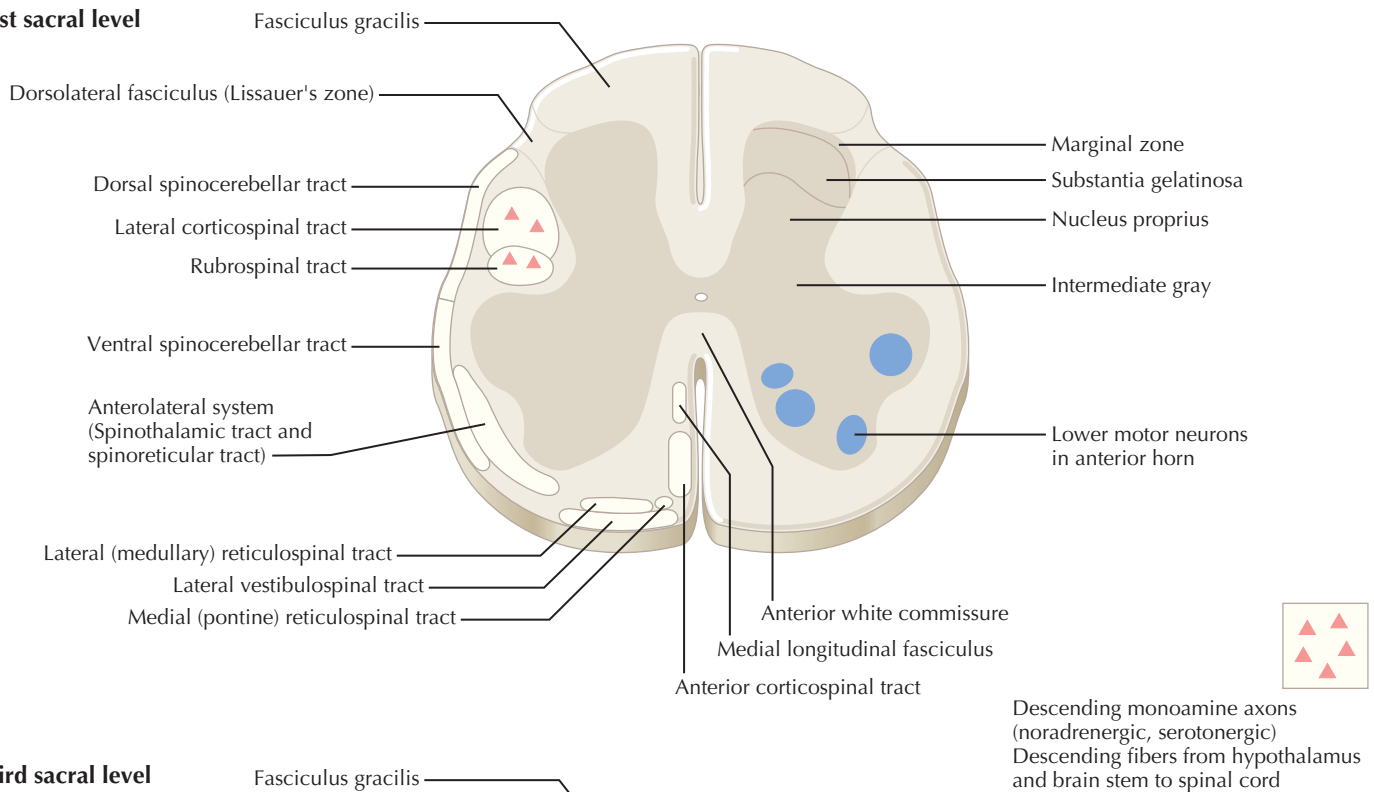
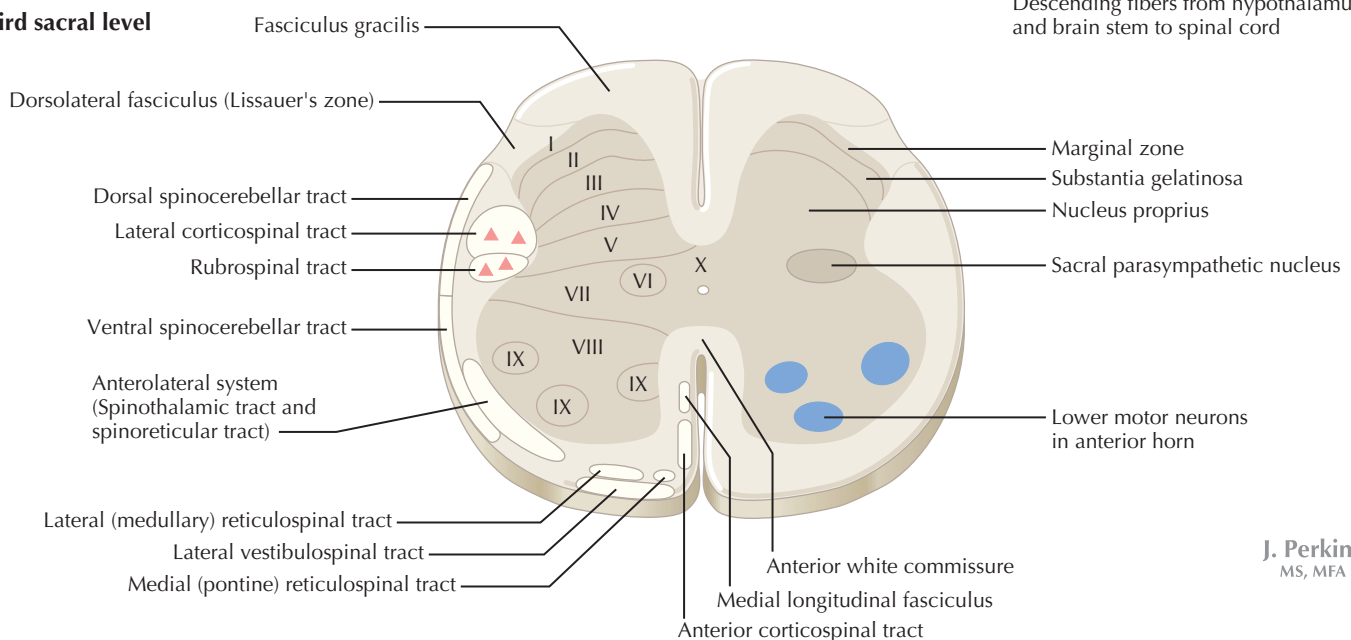
**J. Perkins**  
MS, MFA

## 10.4 SPINAL CORD LEVELS: CERVICAL, THORACIC, LUMBAR, AND SACRAL (continued)

### CLINICAL POINT

The central canal of the spinal cord is ordinarily a closed remnant of former neural tube development and in the adult does not convey or produce cerebrospinal fluid. However, a developmental defect may result in the formation of a syrinx in the central canal region of the spinal cord, either alone or in the presence of an obstruction of the foramen magnum (with Arnold-Chiari malformation). This condition, called syringomyelia, occurs mainly at a lower cervical or a

thoracic level. The distinguishing feature is destruction of the axons in the anterior white commissure, resulting in a dissociated sensory loss of pain and temperature sensation at the levels of the syrinx, with preservation of epicritic sensation (dorsal columns and the dorsolateral funiculus are usually preserved). If the syrinx extends laterally, it most likely will involve adjacent LMNs; this manifests as segmental weakness and muscle atrophy. Larger lesions may extend into the lateral funiculus and damage the descending UMN systems (the corticospinal and rubrospinal tracts), causing ipsilateral spastic paresis below the level of the lesion. Syringomyelia is sometimes accompanied by kyphoscoliosis and pain in the region of the neck and arms. The syrinx may extend to the brain stem (syringobulbia) and produce damage to lower brain stem structures.

**First sacral level****Third sacral level**

**J. Perkins**  
MS, MFA

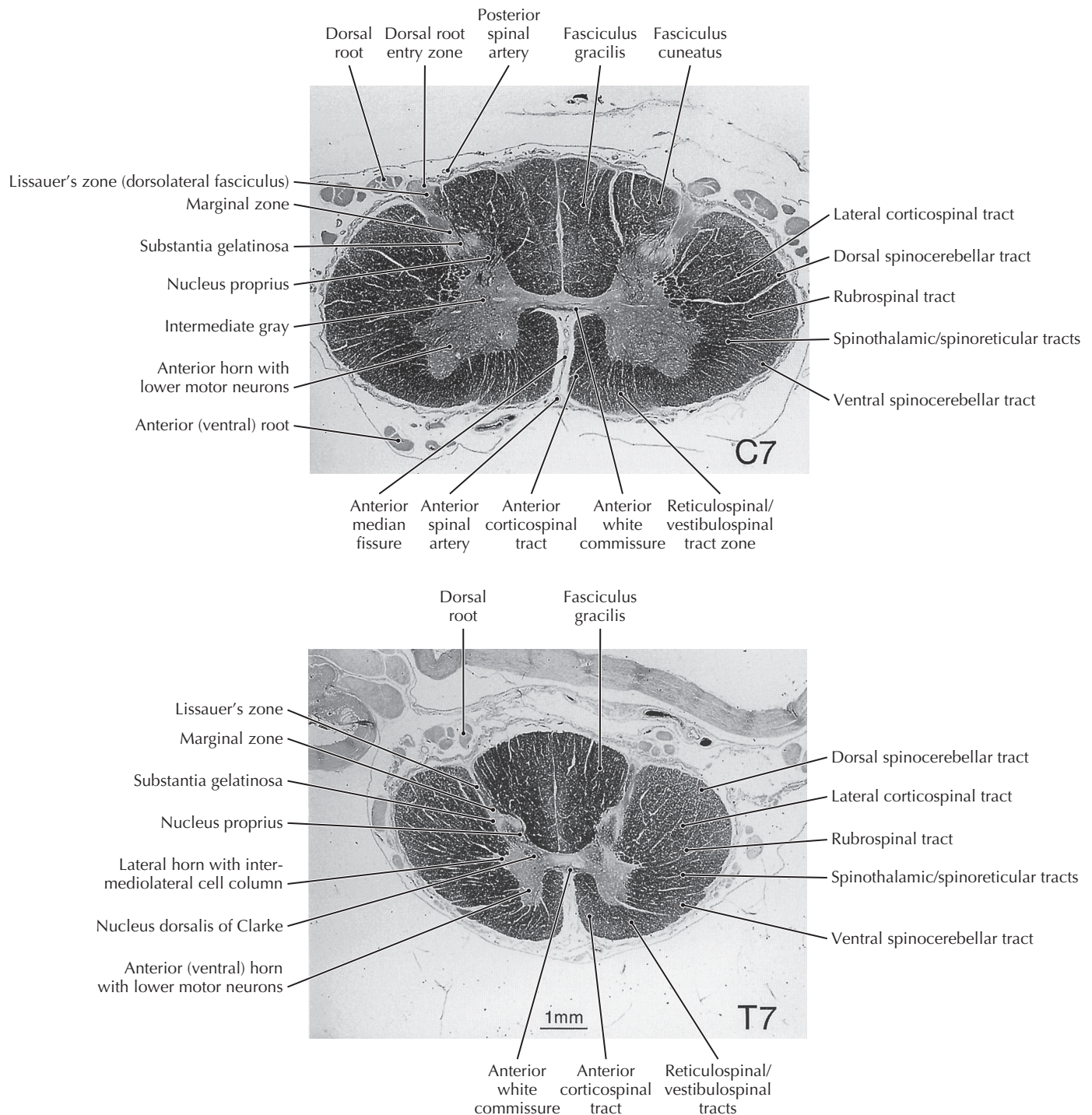
## 10.5 SPINAL CORD LEVELS: CERVICAL, THORACIC, LUMBAR, AND SACRAL (continued)

### CLINICAL POINT

A severe spinal cord crush injury damages local neurons and disrupts both the ascending and the descending tracts. Such a lesion at the lumbar level causes flaccid paralysis of muscles (with loss of tone and muscle stretch reflexes) at the damaged levels as the result of LMN injury and spastic paralysis of muscles (with increased tone and muscle stretch reflexes, possible clonus, and extensor plantar responses) in muscles supplied by LMNs below the level of the lesion as the result of damage to the UMN axons in the lateral funiculus. All

sensation is lost below the level of the lesion because of disruption of both dorsal column and anterolateral axons, although some protopathic sensation may remain present, even in the case of a very extensive lesion. A severe crush injury also damages descending axons in both lateral funiculi that help to regulate bowel function, bladder function, and sexual function. The patient initially shows spinal shock syndrome, with unresponsive bowel and bladder; after recovery from spinal shock, a spastic bladder (small, stimulated to empty by reflex, with incontinence) occurs. In addition, voluntary control over erectile function in males is lost, but reflex erection caused by specific sensory stimuli may occur. Severe crush injury at higher levels (cervical) also can disrupt descending axons that regulate sympathetic outflow, resulting in dysregulated blood pressure, Horner's syndrome, and other autonomic symptoms.

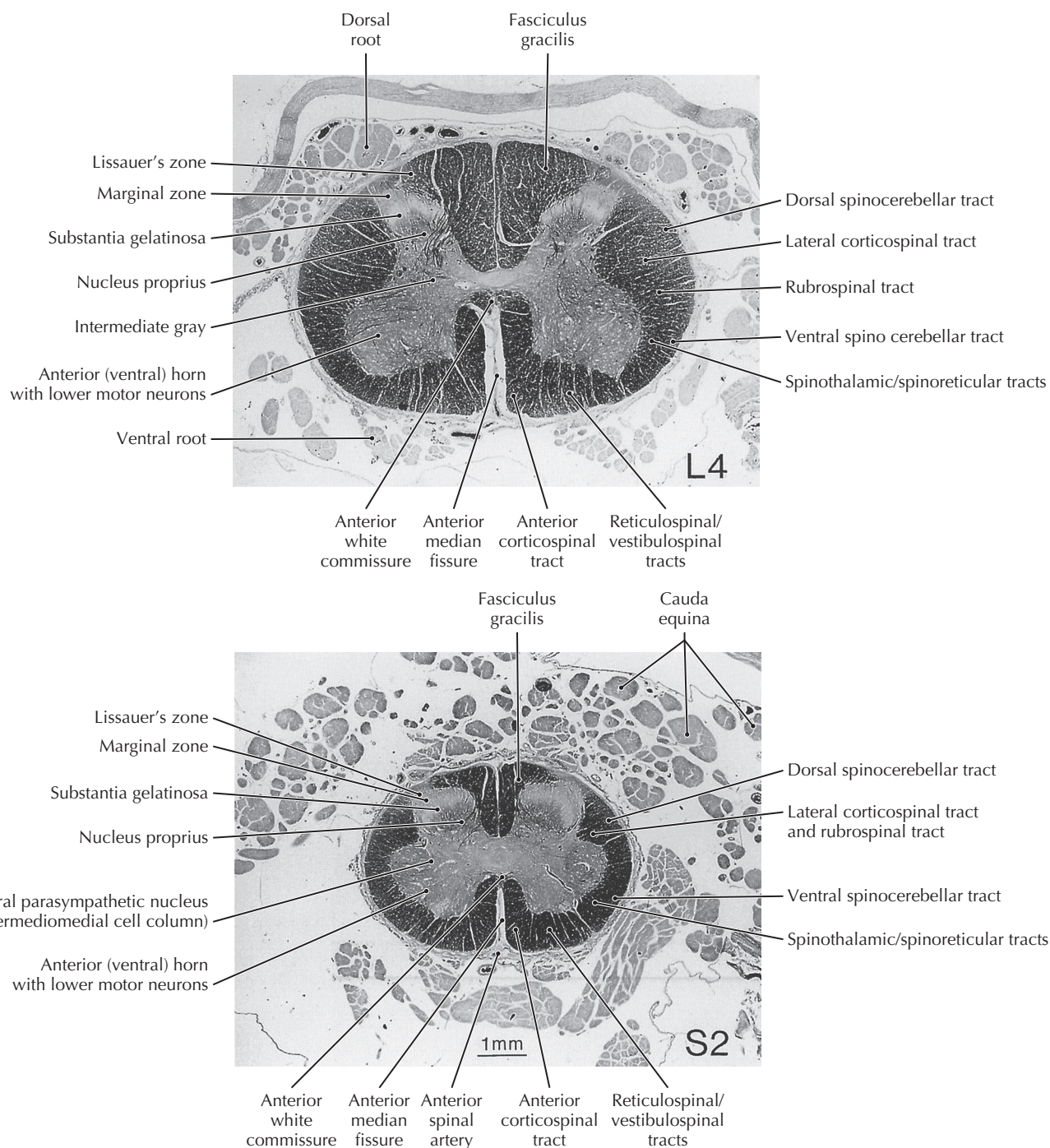




From Paxinos G, Mai JK. The Human Nervous System, ed 2, Philadelphia, Elsevier, 2004 (F7-22).

## 10.6 SPINAL CORD HISTOLOGICAL CROSS SECTIONS

Cross sections through the spinal cord at levels C7 and T7 prepared with a Weigert stain. Major gray matter and white matter zones are labeled.

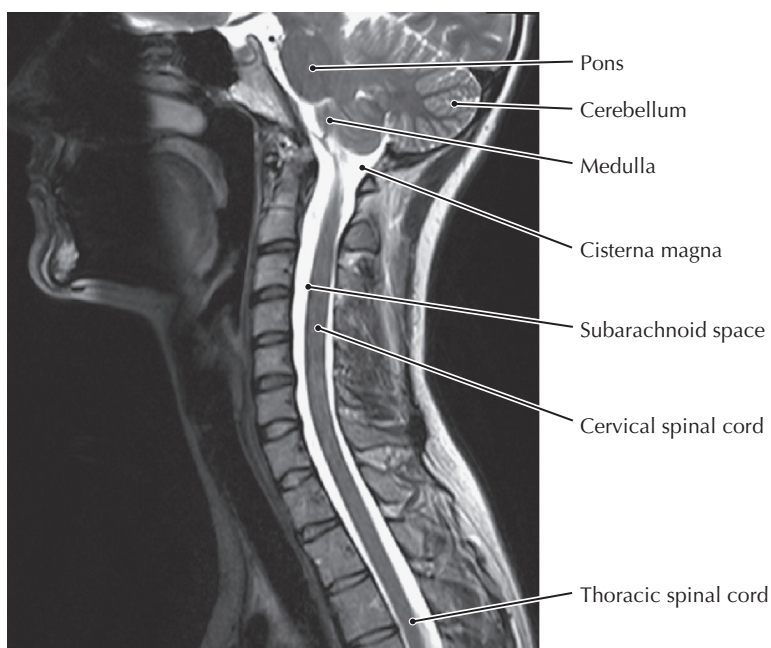


From Paxinos G, Mai JK. The Human Nervous System, ed 2, Philadelphia, Elsevier, 2004 (F7-22).

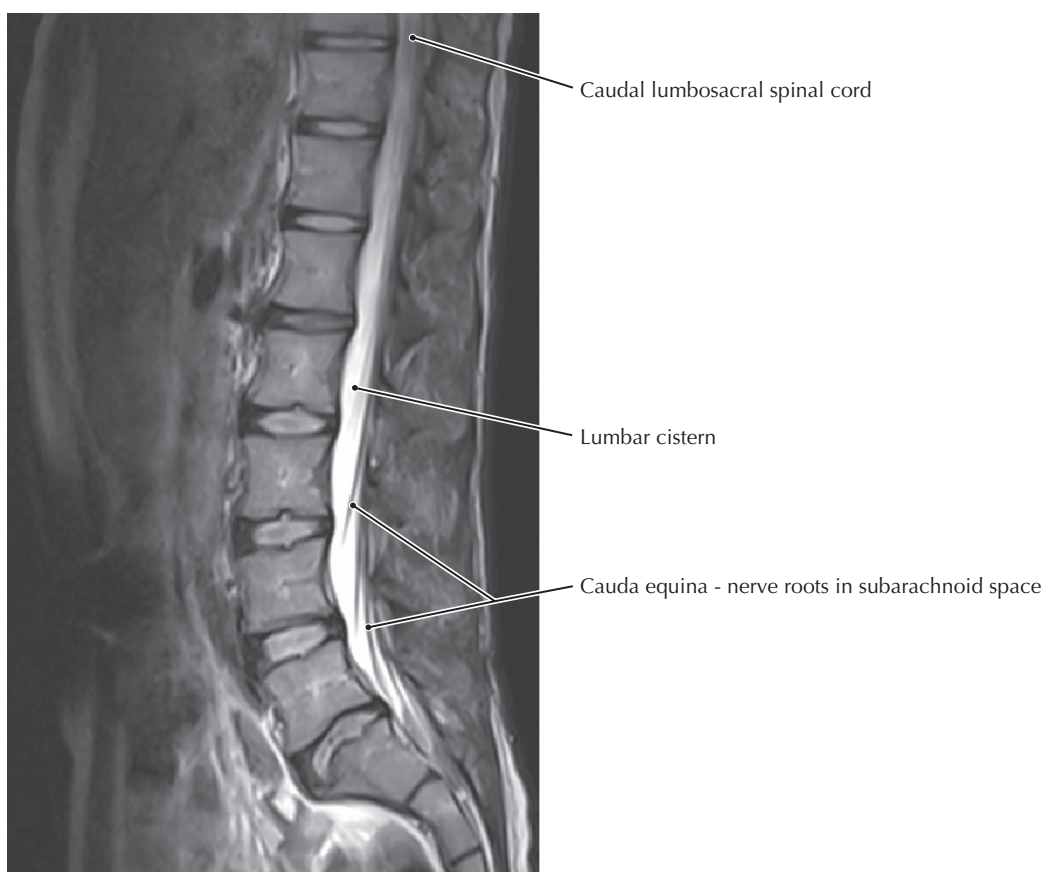
## 10.7 SPINAL CORD HISTOLOGICAL CROSS SECTIONS (CONTINUED)

Cross sections through the spinal cord at levels L4 and S2 prepared with a Weigert stain. Major gray matter and white matter zones are labeled.





**A. Sagittal view - Cervical spine**



**B. Sagittal view - Lumbar spine**

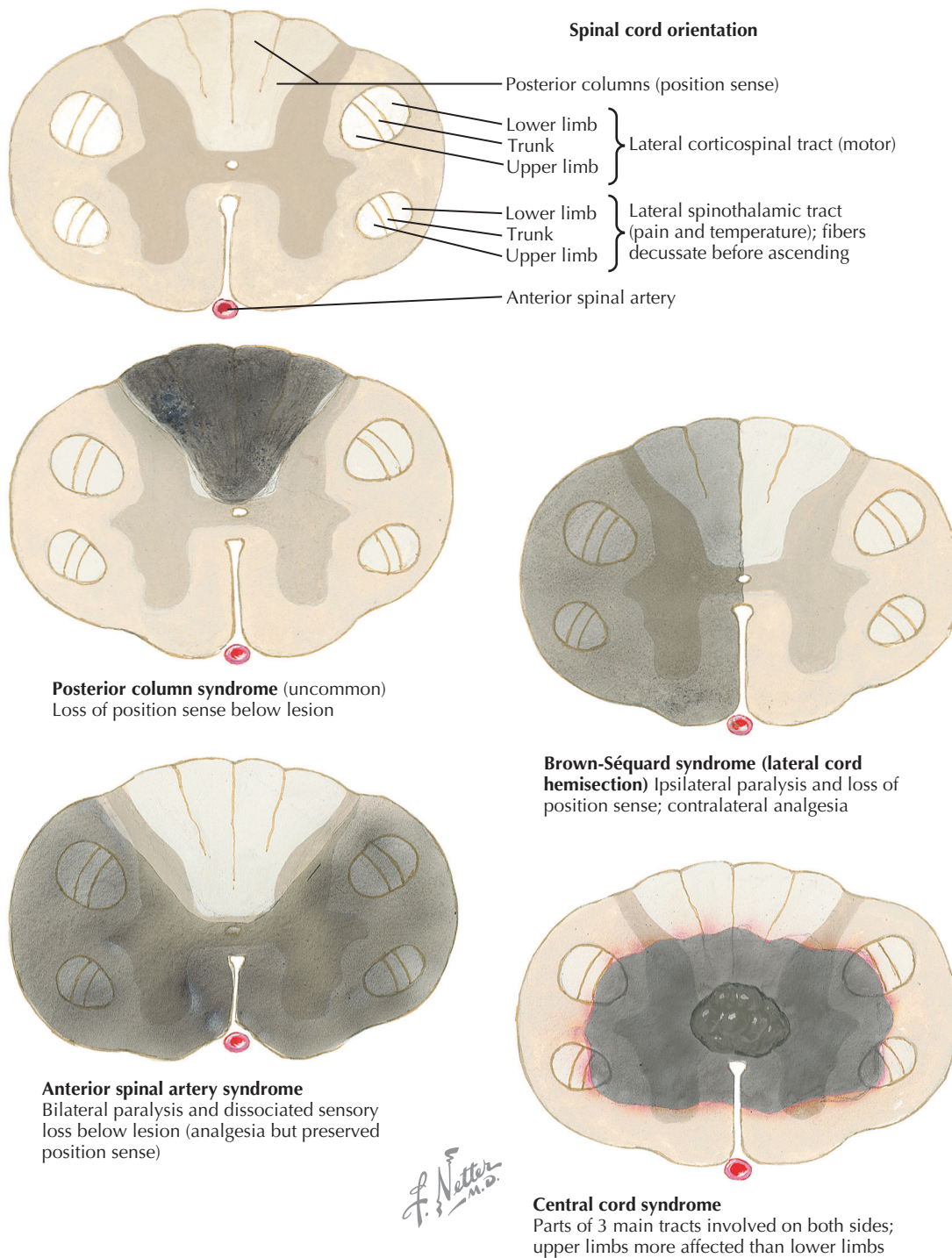
## 10.8 SPINAL CORD IMAGING

These two sagittal illustrations of the spinal cord are T2-weighted magnetic resonance images that reveal the spinal cord as a dark structure and the cerebrospinal fluid (subarachnoid space) as white. **A**, The cervical and thoracic spinal cord. **B**, The lumbosacral spinal cord and the long nerve roots coursing through the subarachnoid space (lumbar cistern) as the cauda equina. Some individual nerve roots can be seen in contrast to the white cerebrospinal fluid.

### CLINICAL POINT

In adults, the sacral segments of the spinal cord are located at the L1 vertebral level. Trauma or a tumor at this specific vertebral level can result in conus medullaris syndrome, which includes paralysis of the muscles of the pelvic floor (LMN damage); a flaccid bladder with overflow incontinence (loss of both parasympathetic input and sensory fibers); constipation and diminished bowel function (loss of parasympathetic control); loss of erectile function (loss of parasympathetic control in males); and “saddle” anesthesia (loss of sensory processing). Pain is sometimes experienced in the gluteal or perineal region. If passing nerve roots of the cauda equina are also damaged, additional sensory and motor impairment of the legs may be seen.

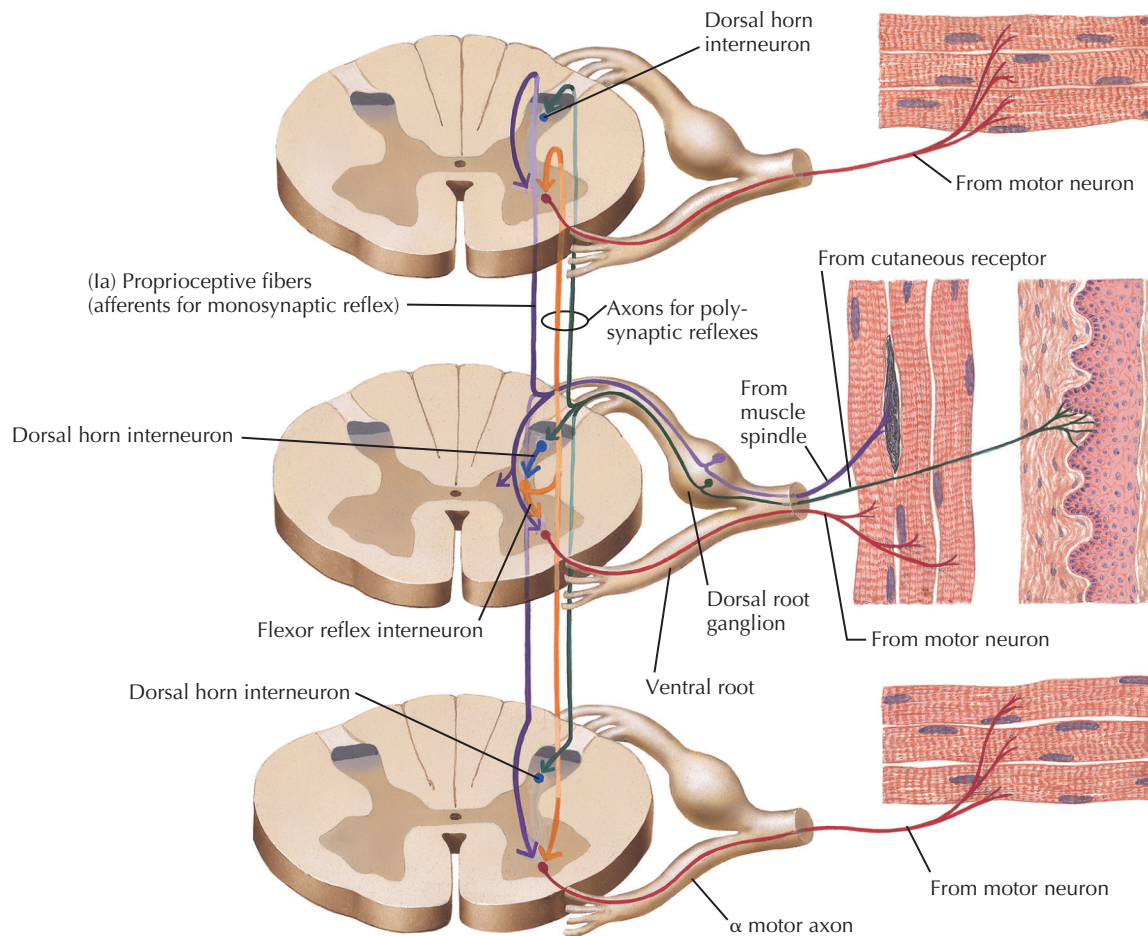




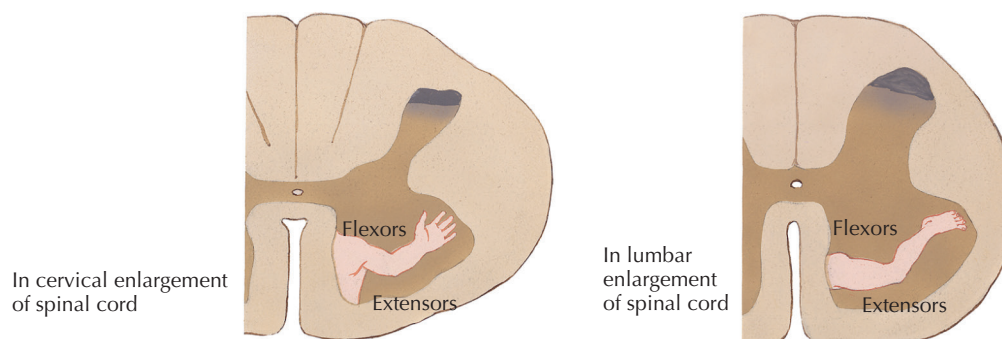
## 10.9 SPINAL CORD SYNDROMES

These illustrations demonstrate a summary of normal spinal cord tract locations and the sites and consequences of incom-

plete spinal cord lesions, including posterior (dorsal) column syndrome, Brown-Séquard lesion (lateral cord hemisection), anterior spinal artery syndrome, and central cord syndrome.



Schematic representation of motor neurons

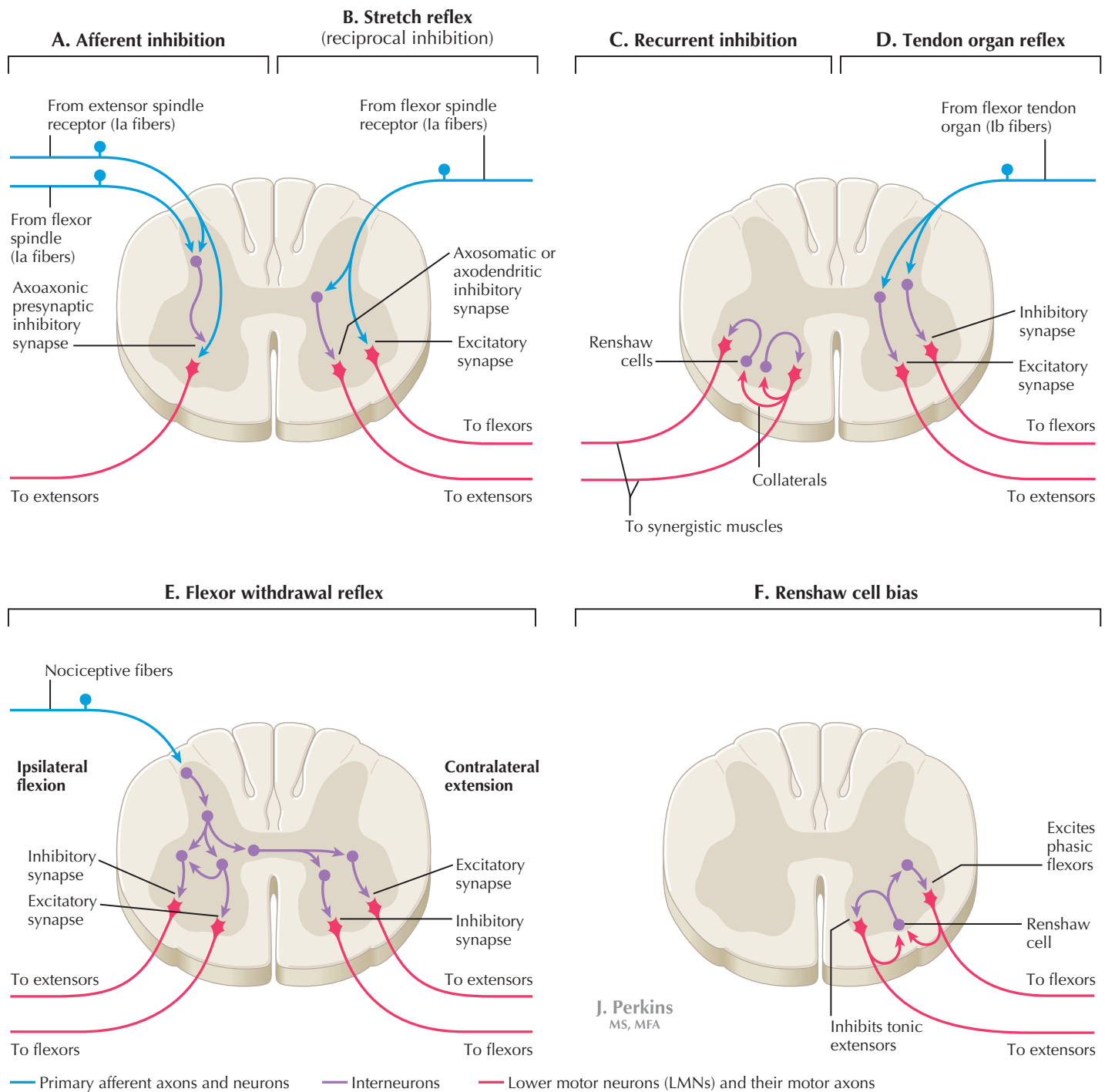


*F. Netter M.D.*

### 10.10 SPINAL CORD LOWER MOTOR NEURON ORGANIZATION AND CONTROL

LMNs are located in the cervical, thoracic, lumbar, and sacral segments of the ventral (anterior) horn of the spinal cord. LMNs also have a medial to lateral and dorsal to ventral organization. LMNs supplying trunk musculature are found medially and ventrally; LMNs innervating more distal musculature are found dorsally and laterally. This organization also is apparent in the topography of UMN control of LMNs. UMN

from the corticospinal system that regulate fine hand and finger movements terminate on dorsal and lateral LMNs. UMN from reticulospinal and vestibulospinal systems that regulate basic truncal tone and posture terminate on ventral and medial LMNs. Reflex pathways regulate LMN activity through monosynaptic (muscle stretch reflex Ia afferents) or polysynaptic (flexor or cutaneous reflex afferents) pathways. Superimposed on this organization is the descending UMN control and coordination of LMNs.



### 10.11 SPINAL SOMATIC REFLEX PATHWAYS

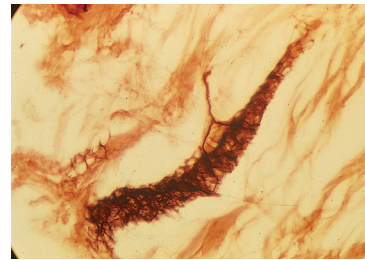
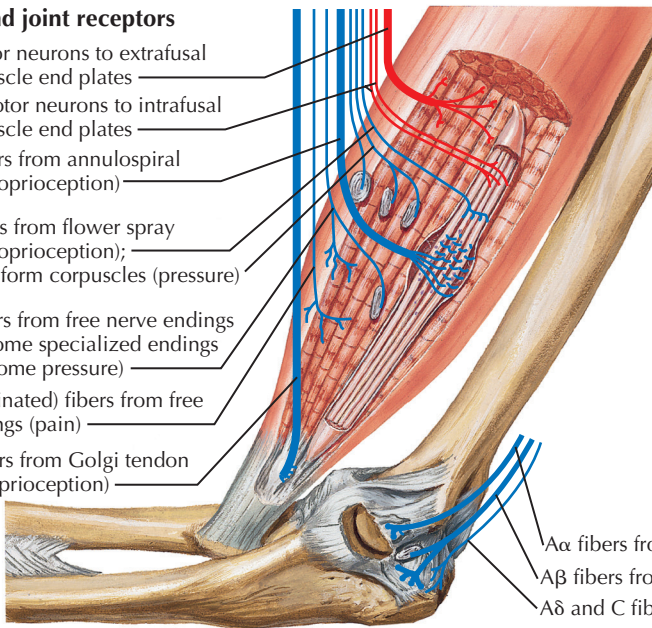
In the muscle stretch reflex, Ia afferents excite the homonymous LMN pool directly and reciprocally inhibit the antagonist LMN pool via Ia inhibitory interneurons. The Golgi tendon organ reflex disynaptically inhibits the homonymous LMN pool and reciprocally excites the antagonist LMN pool. Flexor reflex responses excite a larger pool of LMNs through a great number of interneurons, with reciprocal inhibition of the appropriate antagonist LMNs, to bring about a protective withdrawal response from a noxious stimulus. These reflexes

can extend throughout the entire spinal cord. When an LMN fires an action potential, it excites a Renshaw cell that inhibits that same LMN, thereby ensuring a clean slate for the next set of inputs to that LMN. Renshaw cells receive input from axon collaterals of both flexor and extensor LMNs and in turn exert an inhibitory bias that focuses particularly on the inhibition of extensor LMNs and reciprocal excitation of flexor LMNs. Thus, the Renshaw cells favor flexor movements and help to inhibit extensor movements.

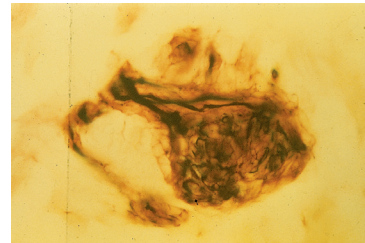


### Muscle and joint receptors

Alpha motor neurons to extrafusal striated muscle end plates  
 Gamma motor neurons to intrafusal striated muscle end plates  
 Ia ( $A\alpha$ ) fibers from annulospiral endings (proprioception)  
 II ( $A\beta$ ) fibers from flower spray endings (proprioception); from paciniform corpuscles (pressure)  
 III ( $A\delta$ ) fibers from free nerve endings and from some specialized endings (pain and some pressure)  
 IV (unmyelinated) fibers from free nerve endings (pain)  
 Ib ( $A\alpha$ ) fibers from Golgi tendon organs (proprioception)

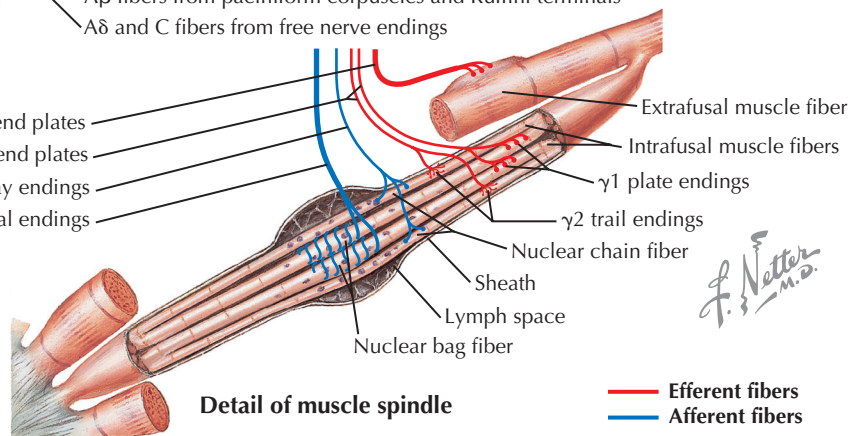


Type III joint receptor (Golgi-like) in a knee ligament. These receptors are high-threshold, slowly adapting, active at far ranges of movement. Fiber stain.



Type I receptor in a joint capsule. These receptors are low-threshold, slowly adapting, usually active at all ranges of movement and positions of the joint. Fiber stain.

Alpha motor neuron to extrafusal muscle fiber end plates  
 Gamma motor neuron to intrafusal muscle fiber end plates  
 II ( $A\beta$ ) fiber from flower spray endings  
 Ia ( $A\alpha$ ) fiber from annulospiral endings



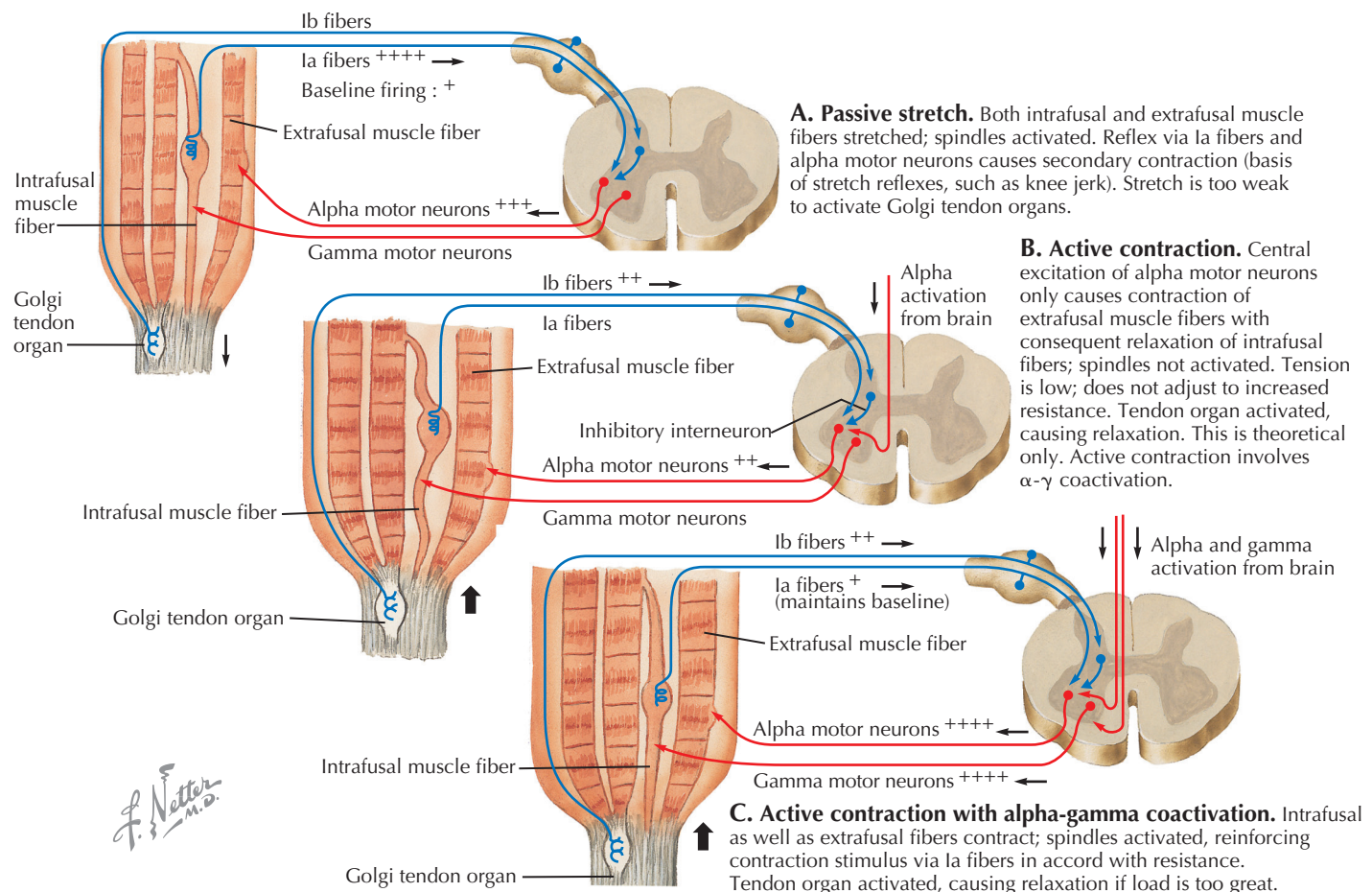
## 10.12 MUSCLE AND JOINT RECEPTORS AND MUSCLE SPINDLES

Joints are innervated by a host of afferent receptors, including bare nerve endings, Golgi-type endings, paciniform endings, Ruffini-like endings, and other encapsulated endings. Golgi tendon organs innervate tendons and respond to stretch with increased discharge, causing disynaptic inhibition of the LMNs that contract the homonymous muscles at high-threshold activation. Muscle spindles are complex sensory receptors within muscles; they are arranged in parallel with the extrafusal (skeletal) muscle fibers. These receptors contain small intrafusal muscle fibers that are stretched when the skeletal muscle is stretched. The Ia afferent from the muscle spindle excites the homonymous LMN pool monosynaptically and responds to both the length and the velocity (change in length with respect to time) of the extrafusal muscle fiber. These muscle reflexes assist in maintaining homeostasis during contraction and help to regulate muscle tone during movement.

### CLINICAL POINT

Skeletal muscles are supplied by both afferent (sensory) and efferent (motor) nerves and receptors. The sensory fibers are associated mainly

with specialized sensory receptors, the muscle spindles. Muscle spindles are small, encapsulated sensory receptors that lie in parallel with the skeletal muscle fibers (extrafusal fibers). Each spindle contains nuclear bag fibers (innervated mainly by group Ia afferents) and nuclear chain fibers (innervated mainly by group II afferents). These afferents are responsive to the tension on the muscle spindle. The II afferents report mainly the lengths of the extrafusal fibers with which they are associated, whereas the Ia afferents report both the lengths and the velocities ( $dL/dt$ ). In conjunction with the Ib afferents associated with Golgi tendon organs that report the force exerted on the tendon, Ia and group II muscle afferents provide continuous information to the CNS about the current state of the muscle and the projected changes occurring, based on the velocity response. The skeletal muscle fibers are supplied by motor axons derived from the alpha motor neurons in the ventral horn of the spinal cord. The muscle spindle's nuclear bag and chain fibers have small contractile fibers on either end by which they are anchored into the spindle. These contractile fibers (intrafusal fibers) are innervated by gamma ( $\gamma$ ) LMNs whose cell bodies also are found in the ventral horn of the spinal cord. Descending UMN pathways generally activate both alpha and gamma LMNs (alpha-gamma coactivation), thereby achieving the shortening of the muscle spindle by the gamma LMNs in parallel with the shortening of the extrafusal fibers, keeping the muscle spindle in its dynamic range of sensory activity. Without such coactivation, the muscle spindle afferents would be silent in most ranges of extrafusal muscle contraction.



### 10.13 THE MUSCLE STRETCH REFLEX AND ITS CENTRAL CONTROL VIA GAMMA MOTOR NEURONS

During passive stretch, a muscle stretch reflex excites homonymous LMNs, which results in muscle contraction to restore homeostasis. If active skeletal muscle contraction occurs without the activation of gamma LMNs (theoretical), the muscle spindle “unloads” and the tension on the intrafusal fibers is reduced, resulting in diminished firing of both Ia and II afferents. However, when LMNs contract because of activity in the brain stem’s UMN or because of voluntary corticospinal activity, both alpha LMNs and gamma LMNs are activated together. This process, alpha-gamma coactivation, ensures that the tension on the muscle spindle (through the intrafusal innervation by gamma fibers) adjusts immediately, that is, as the extrafusal muscle contraction occurs (through alpha fiber innervation). Although alpha and gamma LMNs can be modulated separately by specific central neuronal circuits, in normal physiological circumstances they are coactivated. If gamma LMNs are differentially activated in pathological circumstances, increased muscle tone and spasticity may ensue.

#### CLINICAL POINT

The muscle stretch reflex, a mainstay of neurological diagnosis, depends upon the activity of afferents and efferents associated with the muscle spindle and the skeletal muscle (extrafusal) fibers. When a tendon is tapped with a reflex hammer (e.g., the patellar tendon), the skeletal muscle is briefly stretched, as are the muscle spindles lying in parallel with them. The stretch of the muscle spindle puts tension on the equatorial region of the nuclear bag fibers, resulting in a burst of action potentials from the associated Ia afferents. The Ia afferents synapse directly with alpha LMNs in the spinal cord ventral horn, resulting in contraction of the homonymous muscle (quadriceps) and restoration of homeostasis. The Ia afferents also synapse on Ia inhibitory interneurons in the spinal cord, producing reciprocal inhibition of the antagonist muscles (hamstrings). The excitability of the muscle spindles can determine the robustness of the Ia afferent response to stretch. If the muscle spindle is floppy (unloaded), no Ia afferent response is forthcoming when the related tendon is tapped, and no muscle contraction occurs (areflexia or hyporeflexia); if the muscle spindle is on a hair-trigger of heightened responsiveness, as happens when the gamma LMNs are excessively activated, then a very brisk muscle contraction occurs when the related tendon is tapped (hyperreflexia). The latter situation may occur in cases of lesions in the UMN of the spinal cord and brain, which may produce disinhibition of the dynamic gamma LMNs accompanied by hyperreflexia of the muscle stretch reflexes and spasticity of the involved muscles.

# 11

## BRAIN STEM AND CEREBELLUM

### Brain Stem Cross-Sectional Anatomy

- 11.1 Brain Stem Cross-Sectional Anatomy: Section 1
- 11.2 Brain Stem Cross-Sectional Anatomy: Section 2
- 11.3 Brain Stem Cross-Sectional Anatomy: Section 3
- 11.4 Brain Stem Cross-Sectional Anatomy: Section 4
- 11.5 Brain Stem Cross-Sectional Anatomy: Section 5
- 11.6 Brain Stem Cross-Sectional Anatomy: Section 6
- 11.7 Brain Stem Cross-Sectional Anatomy: Section 7
- 11.8 Brain Stem Cross-Sectional Anatomy: Section 8
- 11.9 Brain Stem Cross-Sectional Anatomy: Section 9
- 11.10 Brain Stem Cross-Sectional Anatomy: Section 10
- 11.11 Brain Stem Cross-Sectional Anatomy: Section 11
- 11.12 Brain Stem Cross-Sectional Anatomy: Section 12
- 11.13 Brain Stem Cross-Sectional Anatomy: Section 13
- 11.14 Brain Stem Cross-Sectional Anatomy: Section 14
- 11.15 Brain Stem Arterial Syndromes

### Cranial Nerves and Cranial Nerve Nuclei

- 11.16 Cranial Nerves: Schematic of Distribution of Sensory, Motor, and Autonomic Fibers
- 11.17 Cranial Nerves and Their Nuclei: Schematic View from Above
- 11.18 Cranial Nerves and Their Nuclei: Schematic Lateral View
- 11.19 Nerves of the Orbit
- 11.20 Nerves of the Orbit (Continued)

- 11.21 Extraocular Nerves (III, IV, and VI) and the Ciliary Ganglion: View in Relation to the Eye
- 11.22 Trigeminal Nerve (V)
- 11.23 Innervation of the Teeth
- 11.24 Facial Nerve (VII)
- 11.25 Facial Nerve Branches and the Parotid Gland
- 11.26 Vestibulocochlear Nerve (VIII)
- 11.27 Glossopharyngeal Nerve (IX)
- 11.28 Accessory Nerve (XI)
- 11.29 Vagus Nerve (X)
- 11.30 Hypoglossal Nerve (XII)

### Reticular Formation

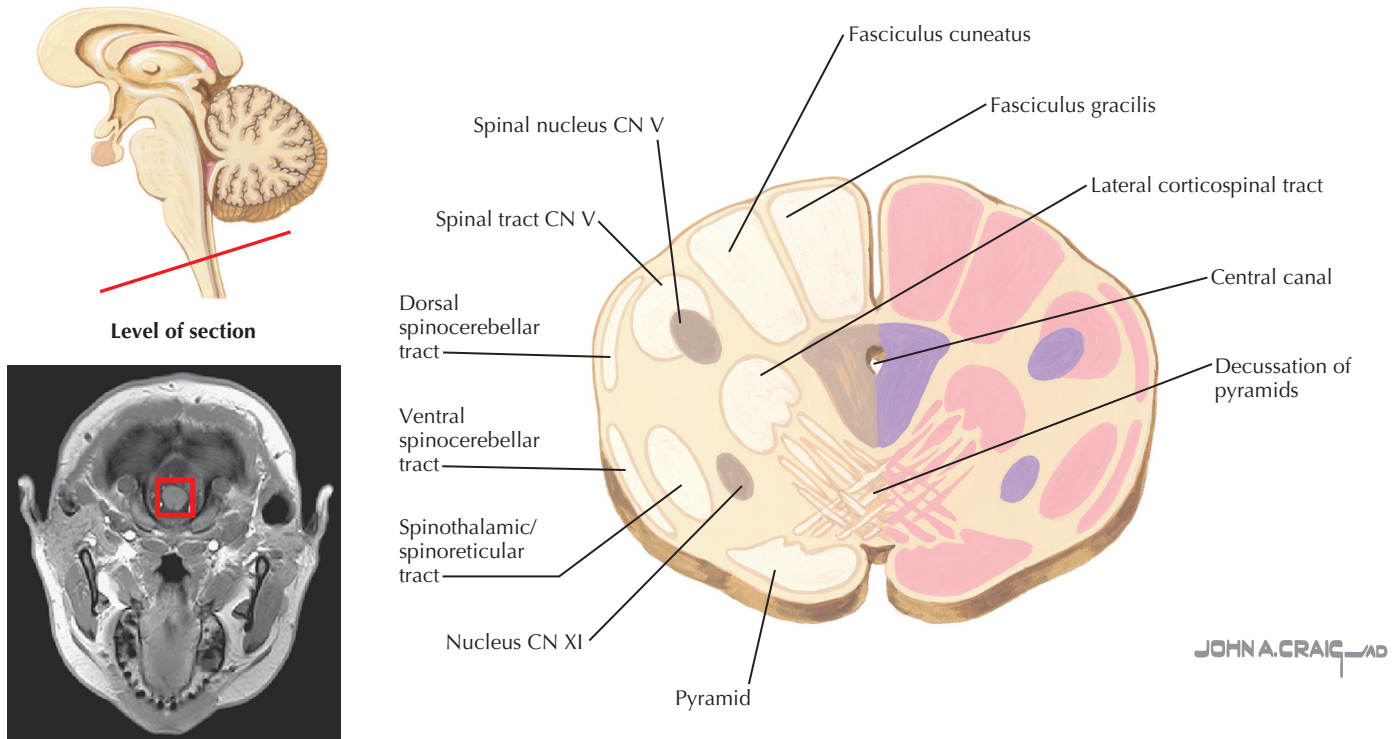
- 11.31 Reticular Formation: General Pattern of Nuclei in the Brain Stem.
- 11.32 Reticular Formation: Nuclei and Areas in the Brain Stem and Diencephalon
- 11.33 Major Afferent and Efferent Connections to the Reticular Formation
- 11.34 Sleep-Wakefulness Control

### Cerebellum

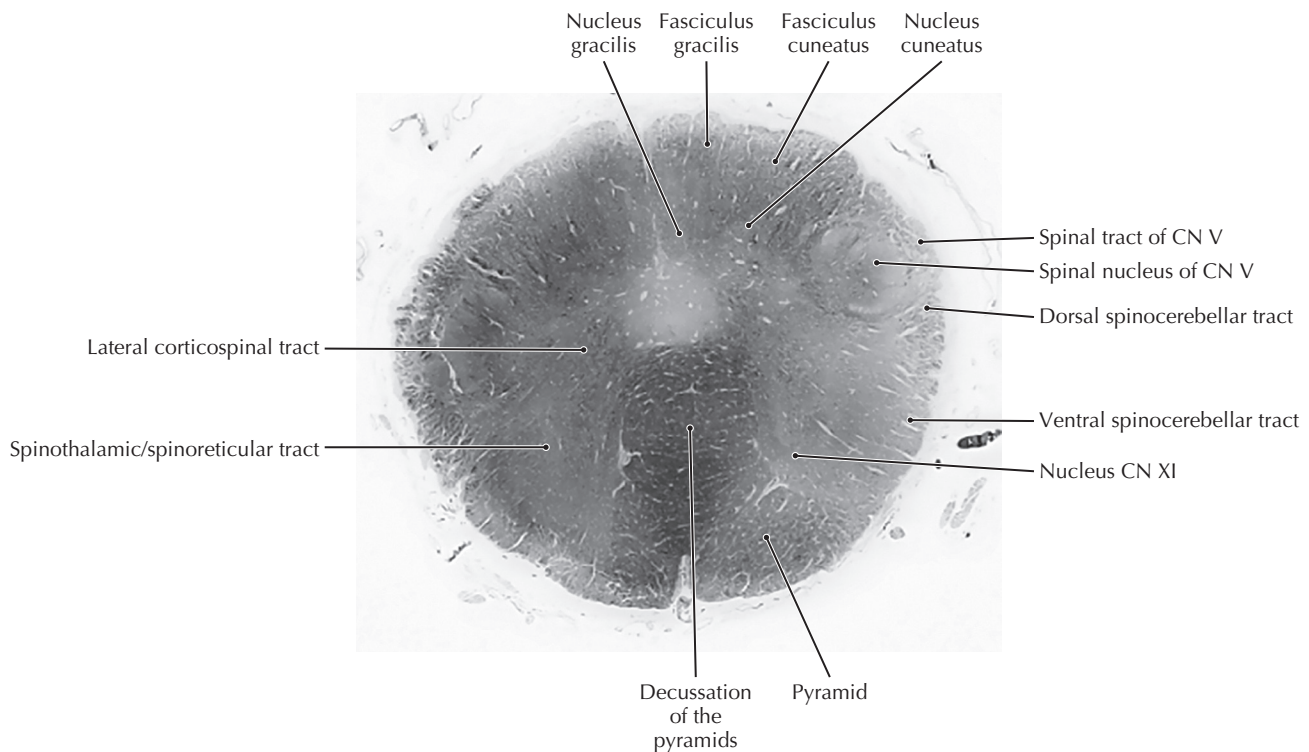
- 11.35 Cerebellar Organization: Lobes and Regions
- 11.36 Cerebellar Anatomy: Lobules
- 11.37 Cerebellar Anatomy: Deep Nuclei and Cerebellar Peduncles



### Medulla-Spinal Cord Transition—Decussation of the Pyramids



Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



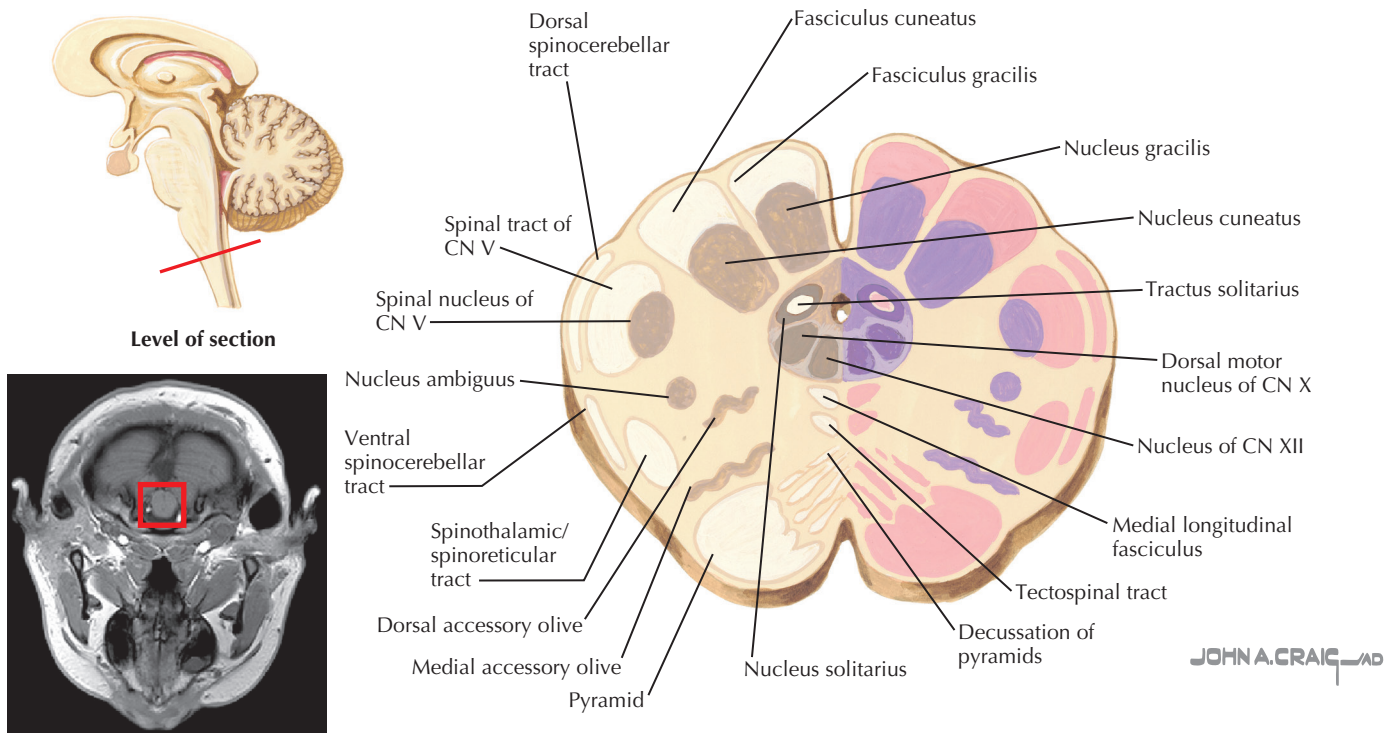
## BRAIN STEM CROSS-SECTIONAL ANATOMY

### 11.1 BRAIN STEM CROSS-SECTIONAL ANATOMY: SECTION 1

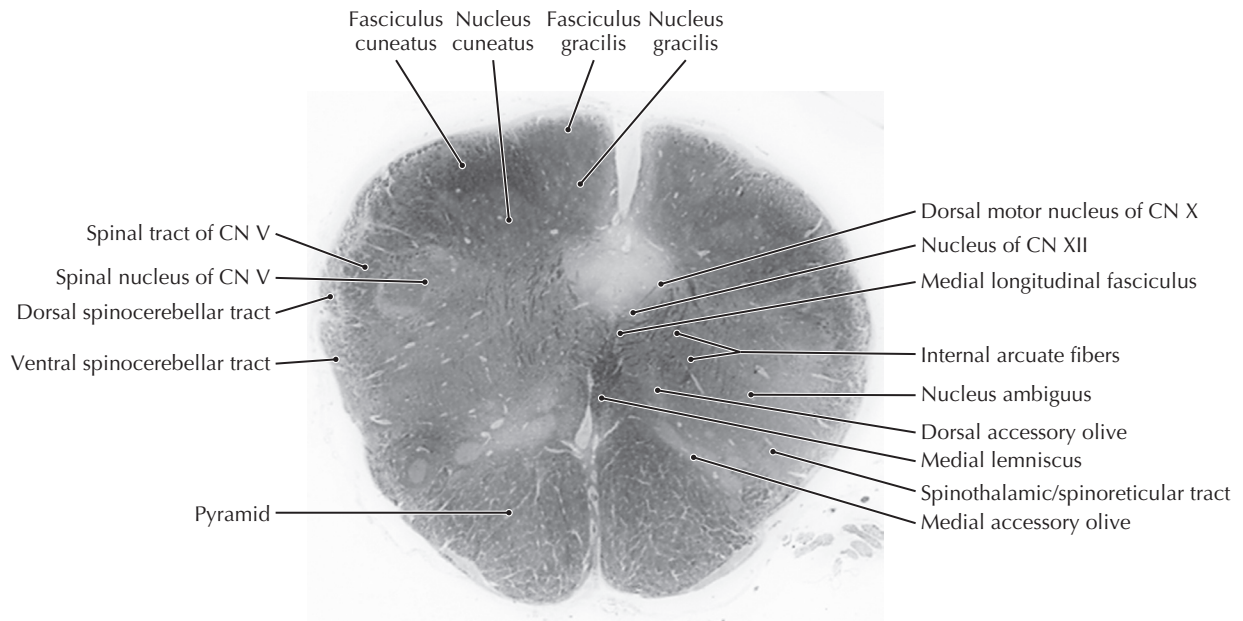
Illustrations of brain stem cross-sections (11.1 through 11.4) are arranged from caudal to rostral, from the spinal-medullary

junction to the rostral mesencephalon-diencephalon junction; T1-weighted magnetic resonance images of the brain stem and surrounding tissue are provided for each level. Corresponding histology cross sections, stained with a fiber stain, are provided of each level. CN, cranial nerve.

## Medulla–Level of the Dorsal Column Nuclei



Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



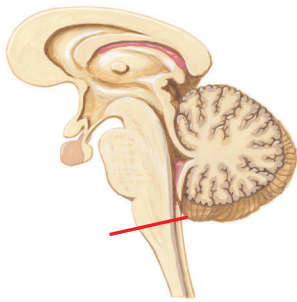
## 11.2 BRAIN STEM CROSS-SECTIONAL ANATOMY: SECTION 2

### CLINICAL POINT

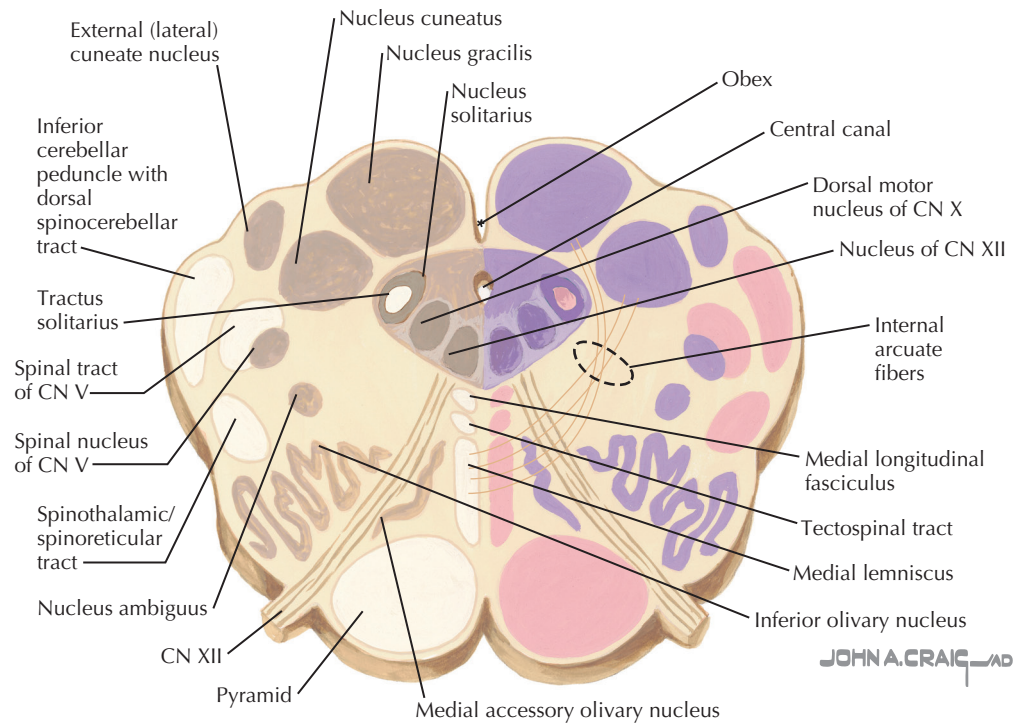
Several groups of LMNs are present in the lower brain stem, including those supplying the tongue (CN XII), the pharynx and larynx (nucleus ambiguus), and the face (CN VII). Neurodegeneration of these brain stem LMNs can occur in bulbar polio, amyotrophic lateral sclerosis, and other LMN diseases. The affected muscles are atrophic and flaccid. Such a condition is called bulbar palsy (or progressive bulbar paralysis), an LMN disorder, accompanied by loss of movement, tone, and reflexes. The tongue is weak and atrophic, and the patient cannot

speak or vocalize (dysarthria or anarthria, not aphasia) and cannot swallow (dysphagia); as a consequence the patient may aspirate in an attempt to swallow. This LMN condition must be distinguished from UMN lesions which, when bilateral, can also result in dysphonia, dysphagia, and weakened bulbar muscles. This UMN condition is called pseudobulbar palsy or spastic bulbar palsy. In this condition, the muscles are not atrophic, and reflexes (jaw jerk and facial reflexes) are brisk. In amyotrophic lateral sclerosis, both LMN and UMN degeneration may occur progressively during the course of the disease. Because the LMNs are the final common pathway to the muscles, the LMN state usually progresses; once the LMNs have degenerated, continuing UMN damage does not make a difference functionally.

### Medulla–Level of the Obex

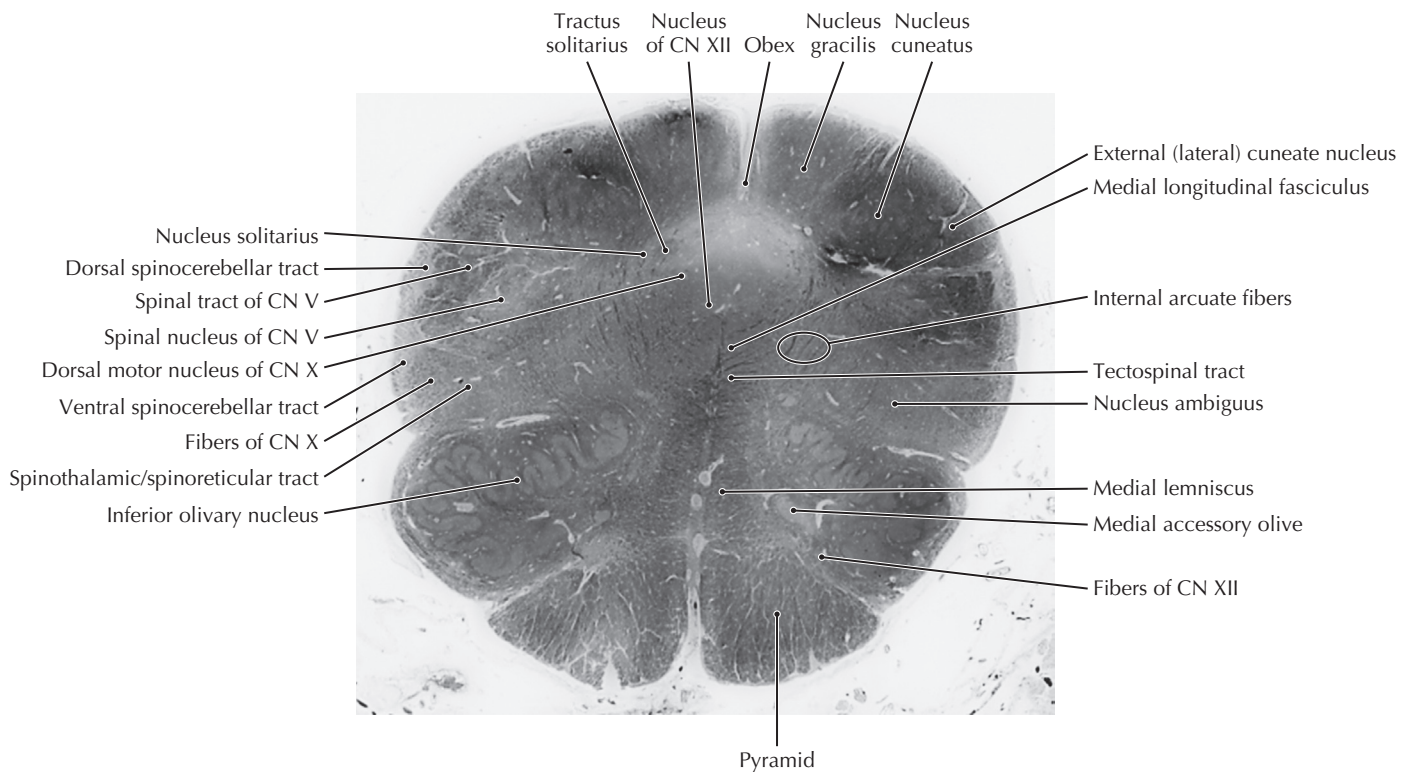


Level of section



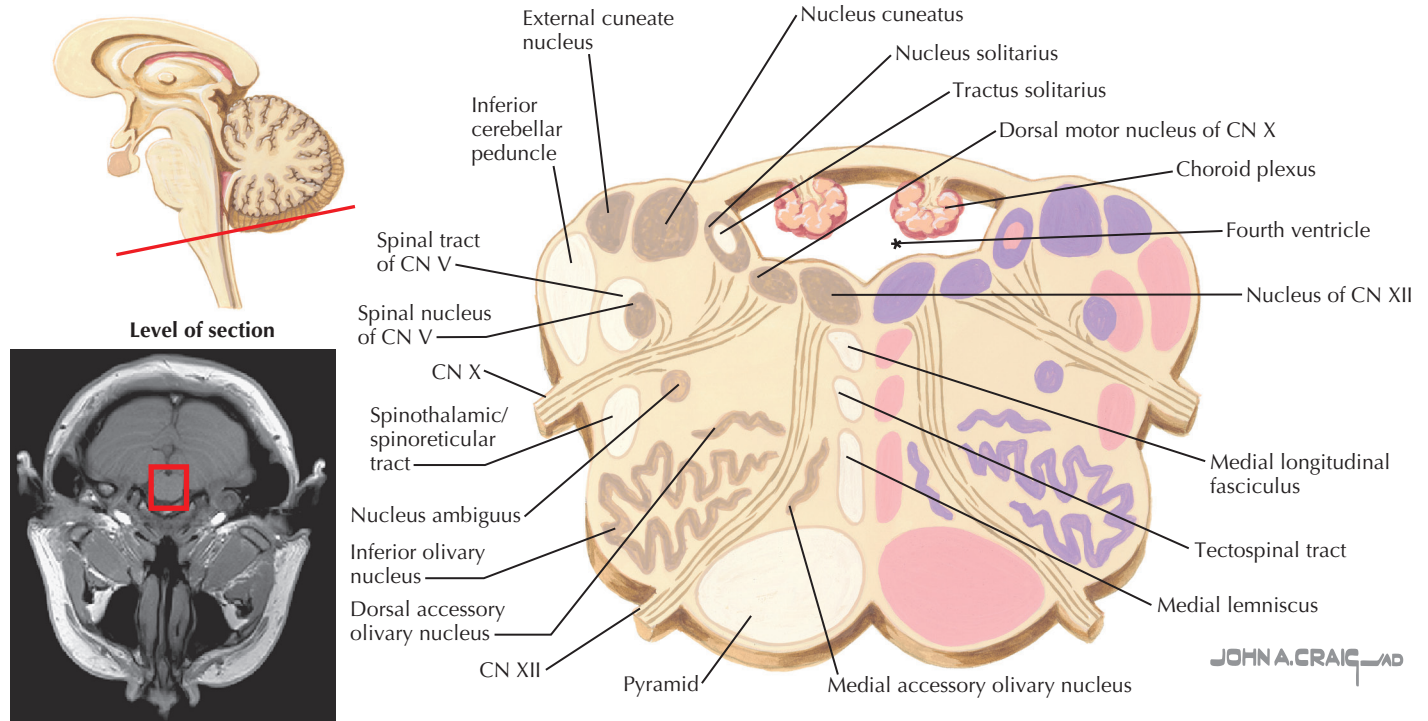
JOHN A. CRAIG AD

Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).

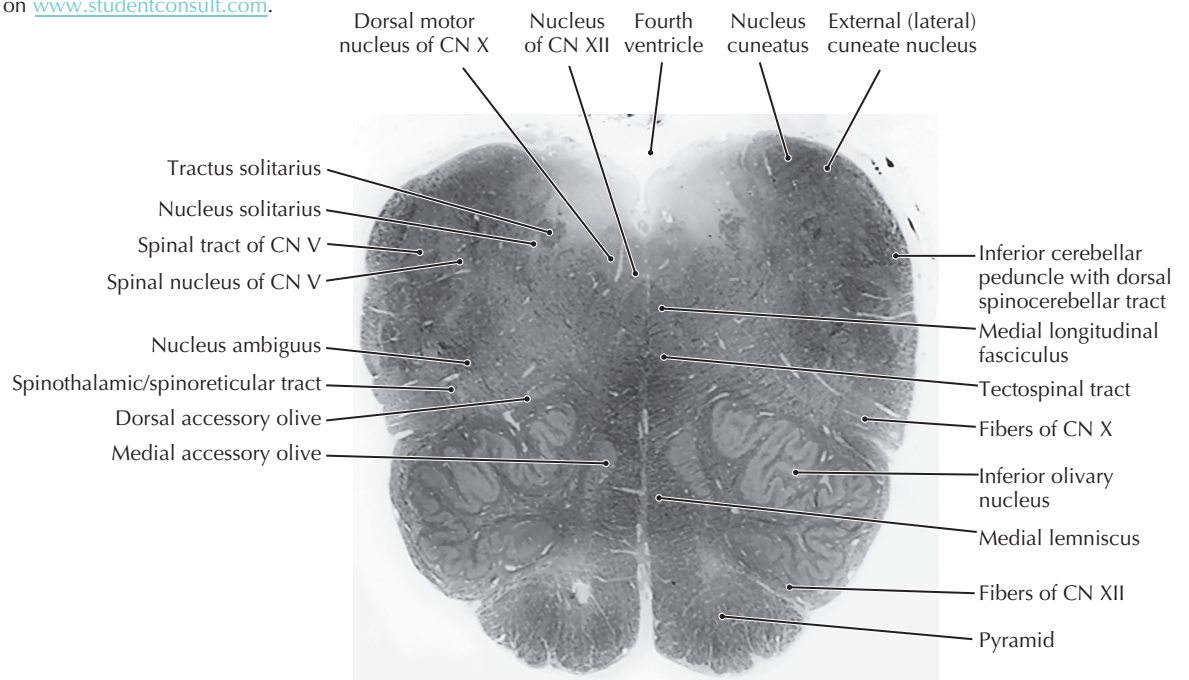




## Medulla–Level of the Inferior Olive



Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



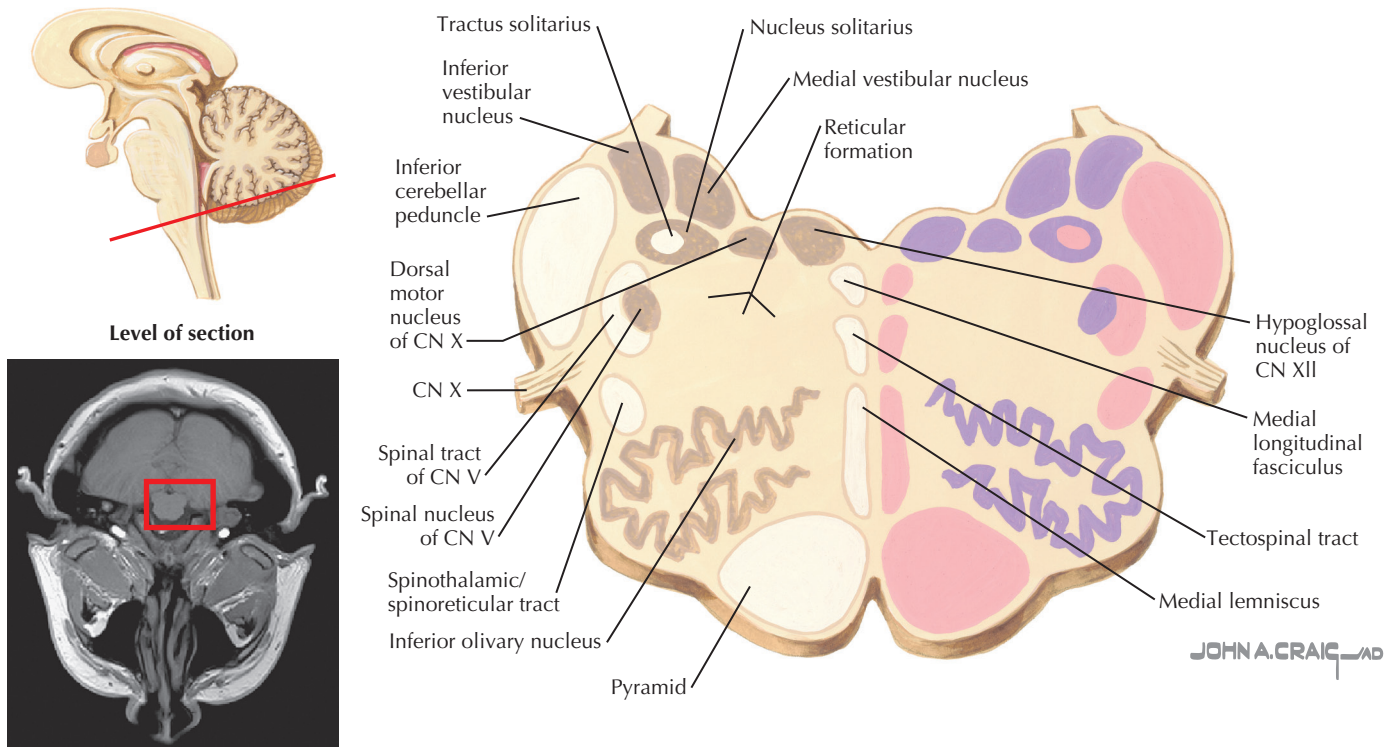
## 11.4 BRAIN STEM CROSS-SECTIONAL ANATOMY: SECTION 4

### CLINICAL POINT

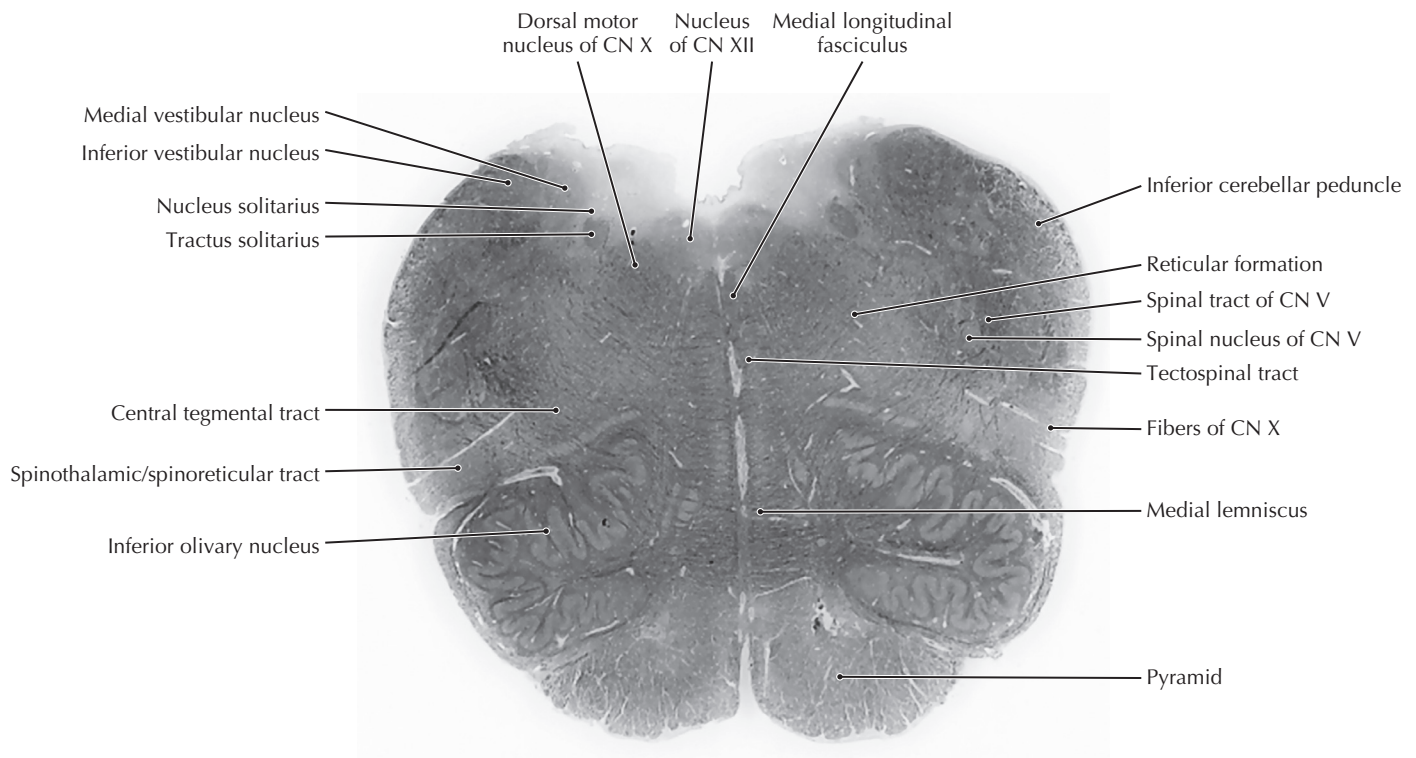
The medulla is supplied with blood by the paramedian and circumferential branches of the anterior spinal artery and the vertebral arteries. A major circumferential branch of the vertebral artery, the posterior inferior cerebellar artery (PICA) supplies a lateral wedge of medulla with blood. A brain stem stroke or an infarct in a vertebral artery or in the PICA produces a complex of symptoms called the lateral medullary syndrome (Wallenberg syndrome), which is caused

by damage to an array of nuclei and tracts. The patient can demonstrate (1) loss of pain and temperature sensation on the ipsilateral side of the face (descending nucleus and tract of V) and the contralateral side of the body (spinothalamic/spinoreticular system); (2) dysphagia and dysarthria (paralysis of ipsilateral pharyngeal and laryngeal muscles resulting from damage to the ipsilateral nucleus ambiguus); (3) ataxia of the limbs and falling to the ipsilateral side (inferior cerebellar peduncle and its afferent tracts); (4) vertigo with nausea, vomiting, and nystagmus (vestibular nuclei); and (5) ipsilateral Horner's syndrome, with ptosis, miosis, and anhidrosis (descending axons from the hypothalamus to the T1–T2 intermediolateral cell column of the spinal cord).

### Medulla–Level of the CN X and the Vestibular Nuclei

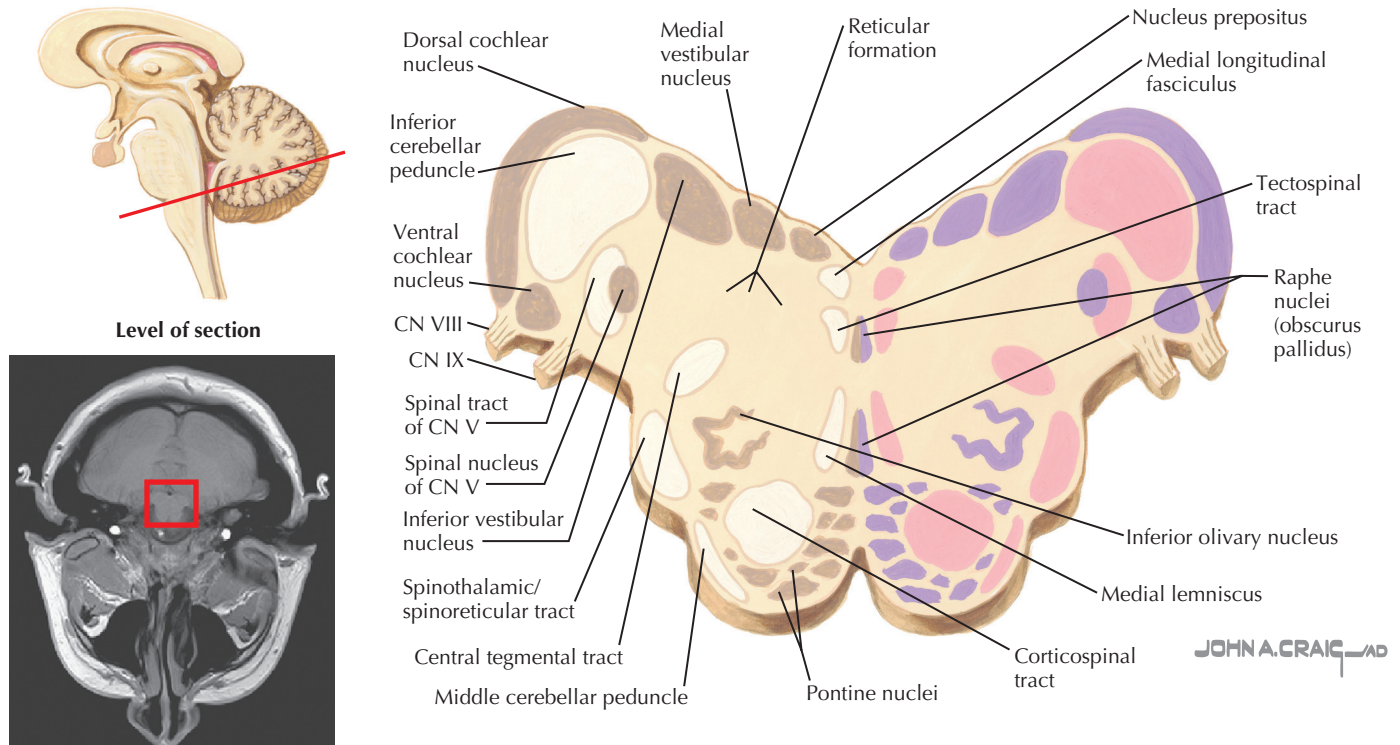


Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).

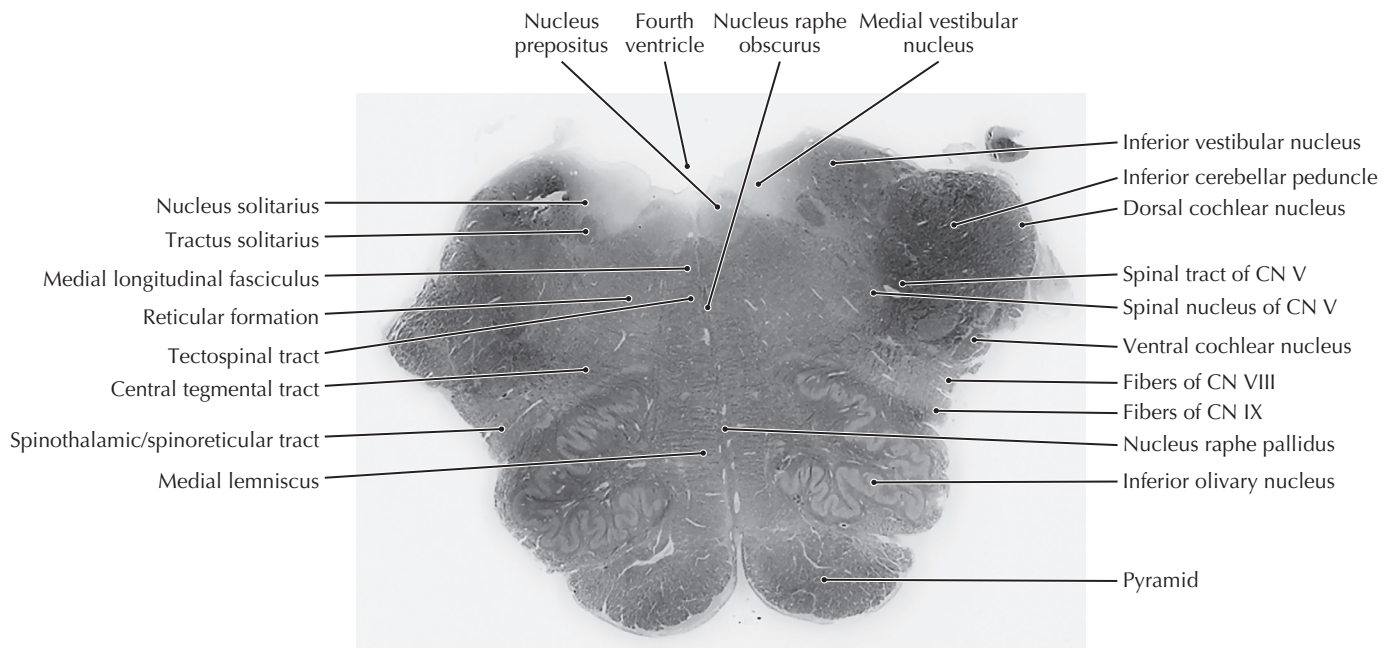




## Medullo-Pontine Junction–Level of the Cochlear Nuclei



Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



## 11.6 BRAIN STEM CROSS-SECTIONAL ANATOMY: SECTION 6

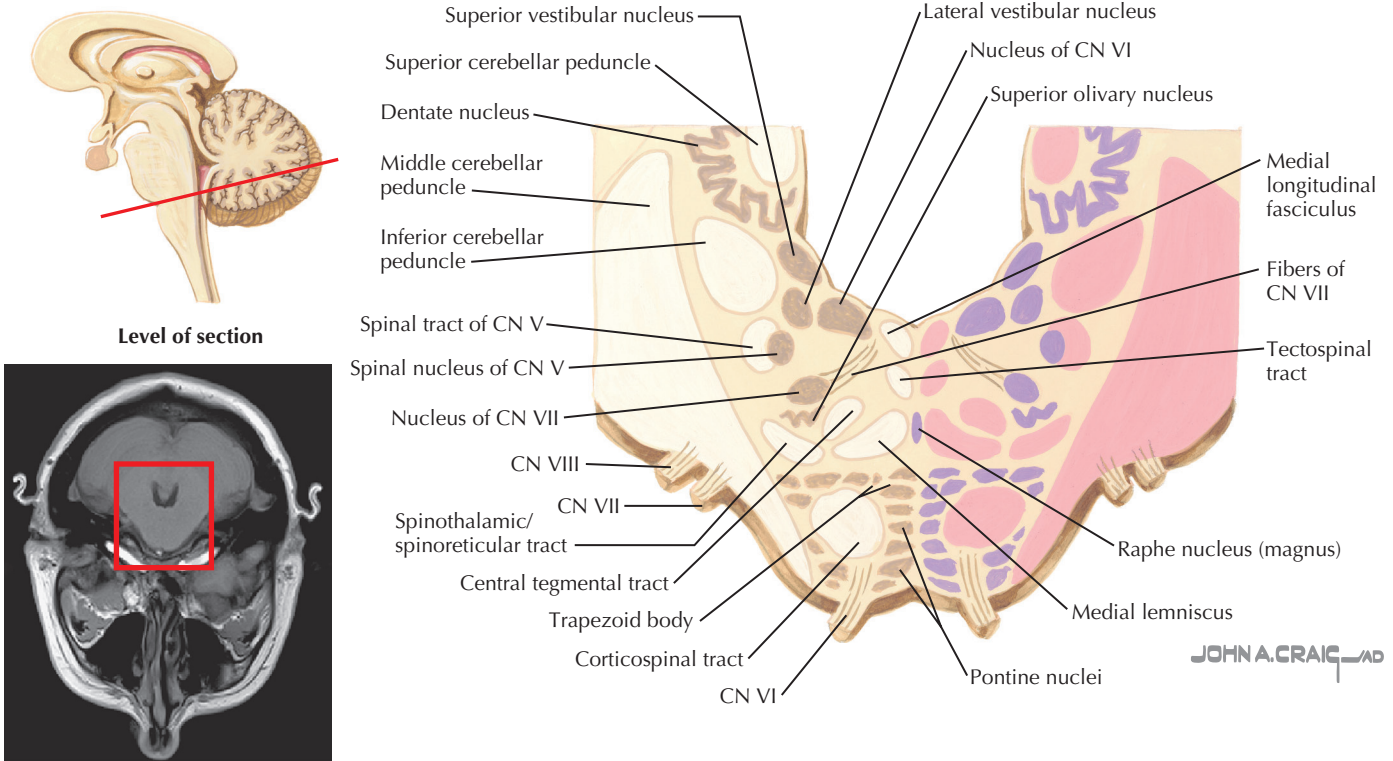
### CLINICAL POINT

Occlusion of a paramedian branch of the basilar artery in the lower pons results in medial inferior pontine syndrome. This vascular syndrome causes (1) contralateral hemiparesis (corticospinal system) and drooping of the contralateral lower face (corticobulbar fibers); (2) loss

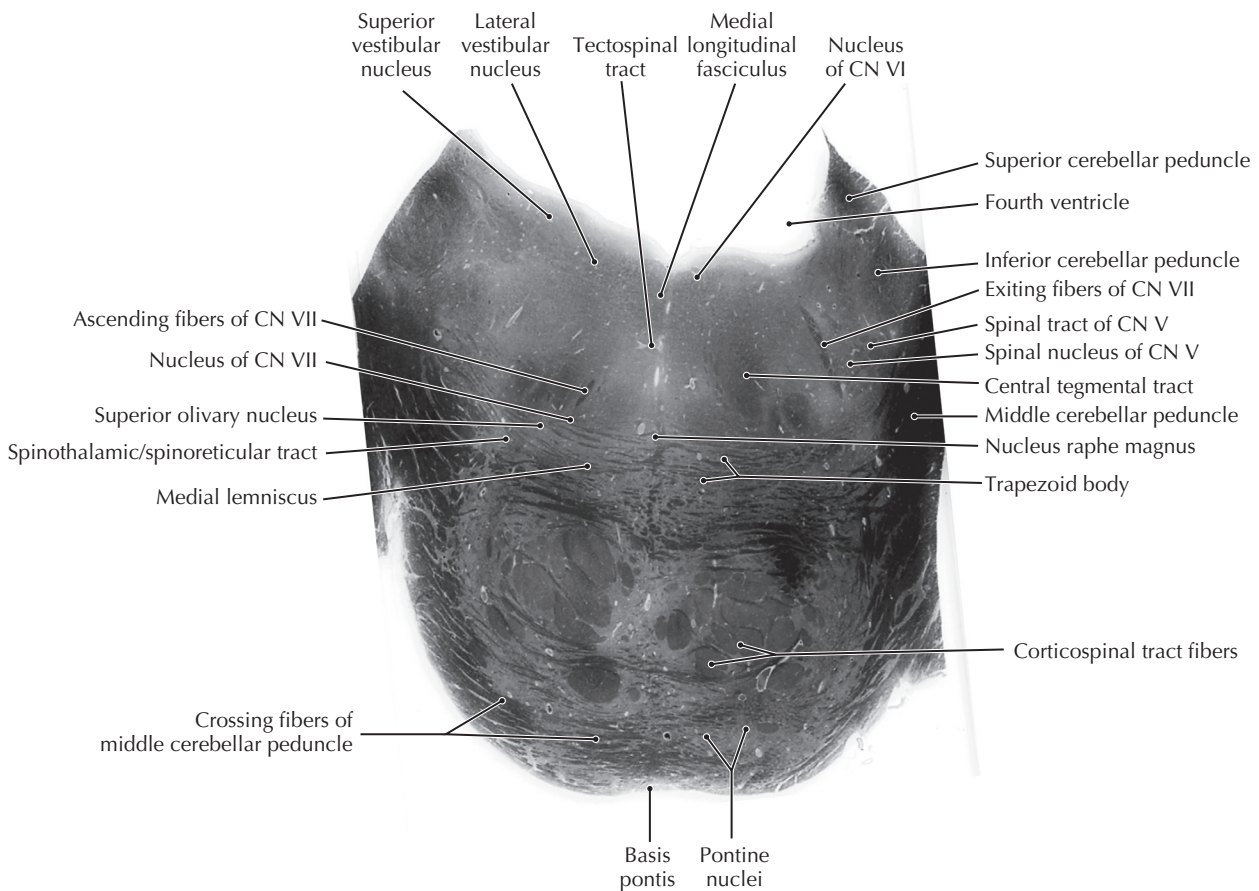
of fine, discriminative touch, vibratory sensation, and joint position sense on the contralateral body that is more severe in the upper extremity (medial lemniscus); (3) limb ataxia and gait ataxia (pontine nuclei and bilateral crossing connections going into the middle cerebellar peduncles); (4) paralysis of lateral gaze by the ipsilateral eye, with resultant diplopia (abducens nerve, nucleus); (5) paralysis of conjugate gaze to ipsilateral side, with preservation of convergence (parapontine reticular formation); and (6) diplopia on attempted lateral gaze to the contralateral side, called internuclear ophthalmoplegia (medial longitudinal fasciculus).



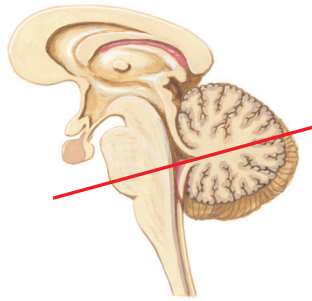
### Pons-Level of the Facial Nucleus



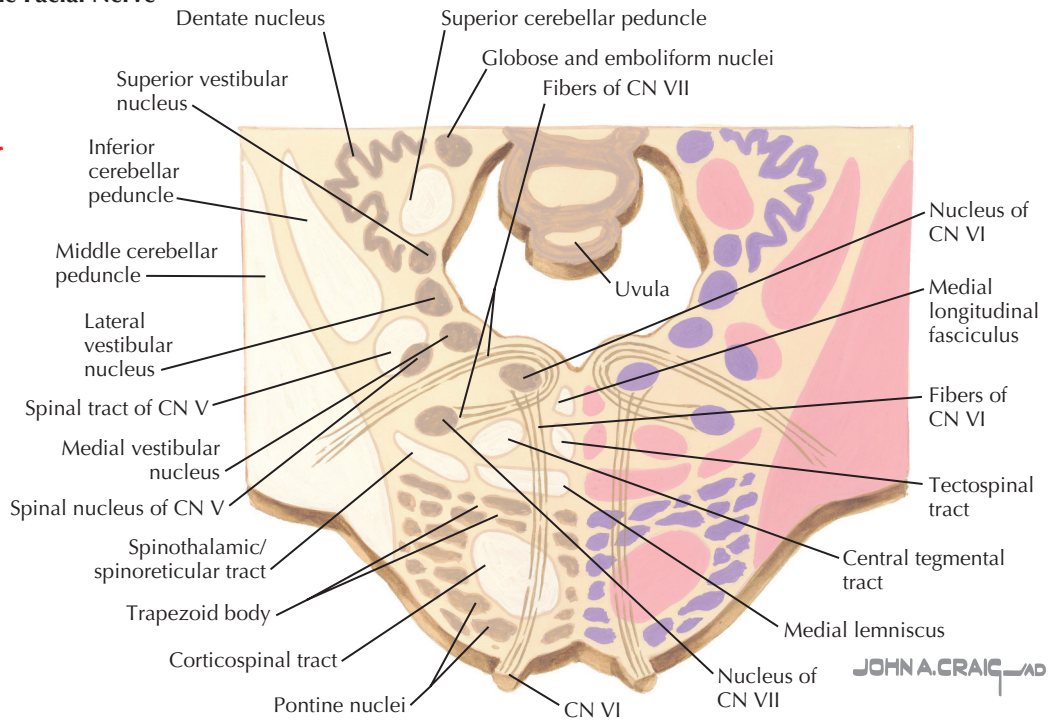
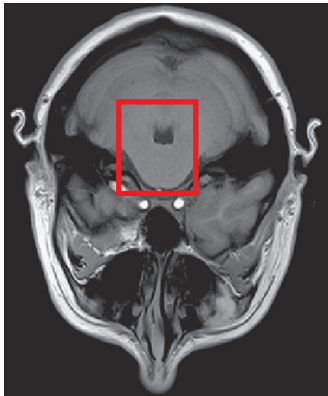
Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



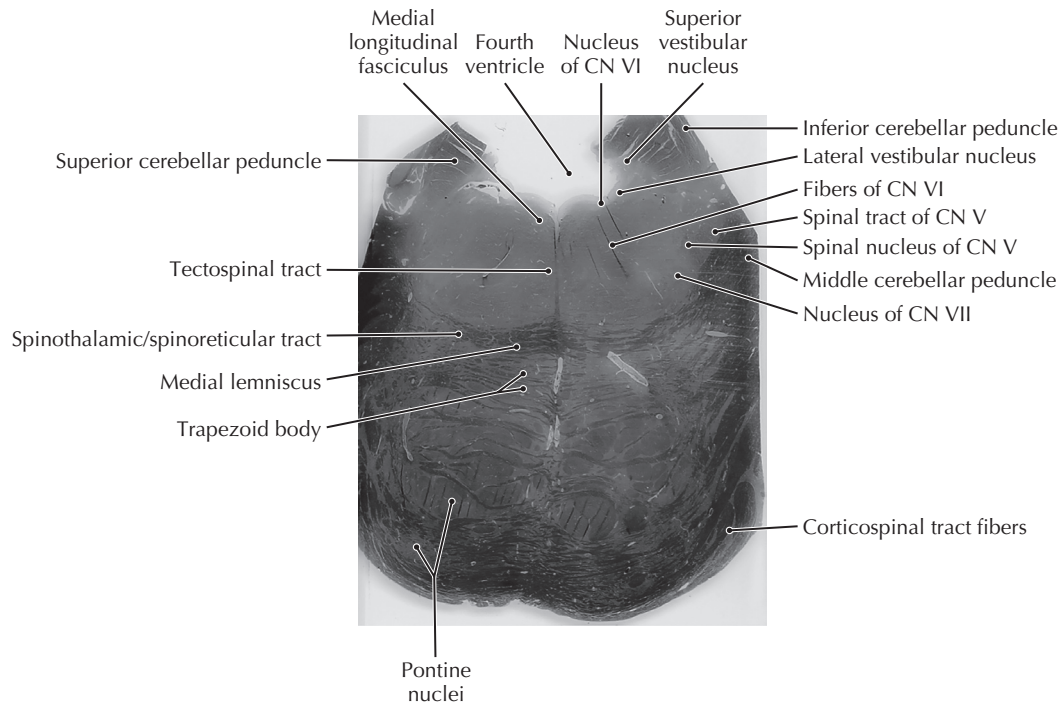
## Pons—Level of the Genu of the Facial Nerve



Level of section



Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



## 11.8 BRAIN STEM CROSS-SECTIONAL ANATOMY: SECTION 8

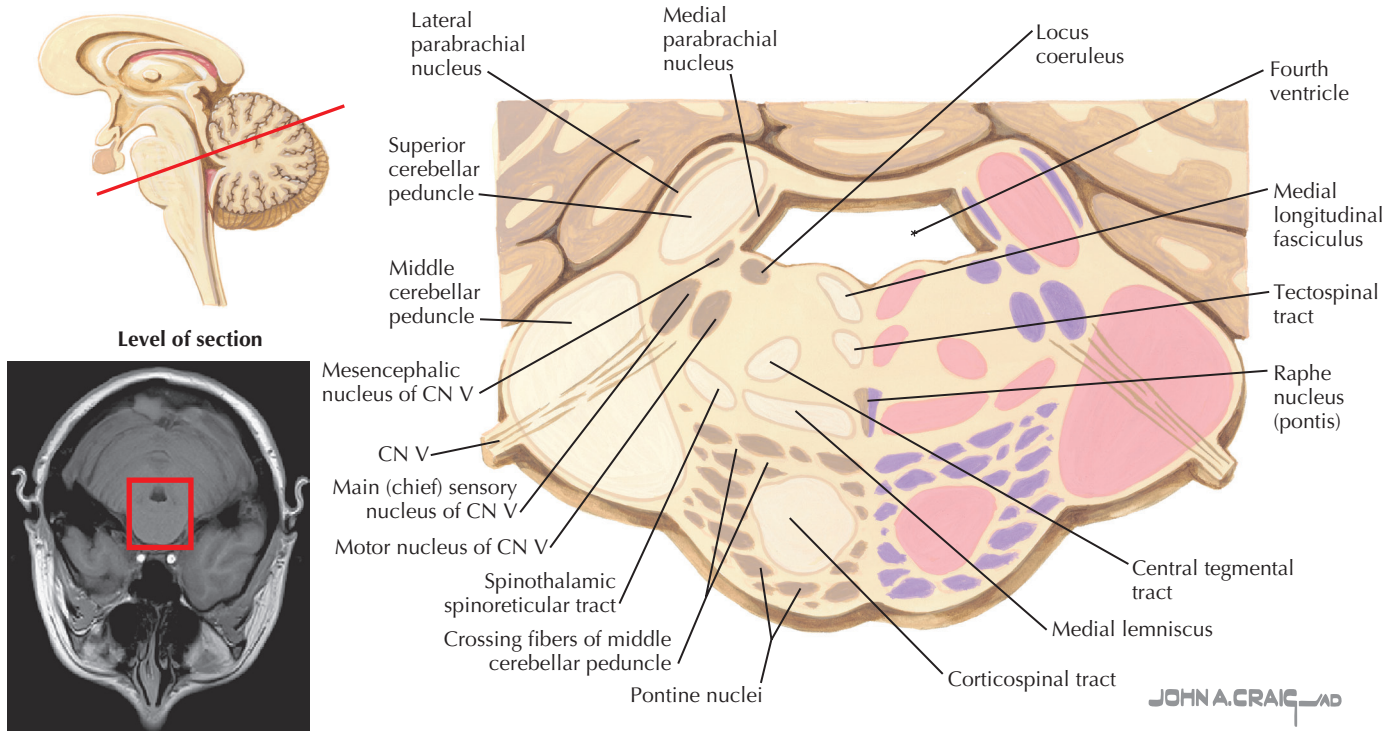
### CLINICAL POINT

The pons is a common site for a hemorrhagic stroke. A pontine hemorrhage is commonly large and lethal. When not fatal, such a hemorrhage may result in the rapid progression of (1) total paralysis (quadriplegia); (2) decerebrate posturing (extensor posturing) caused

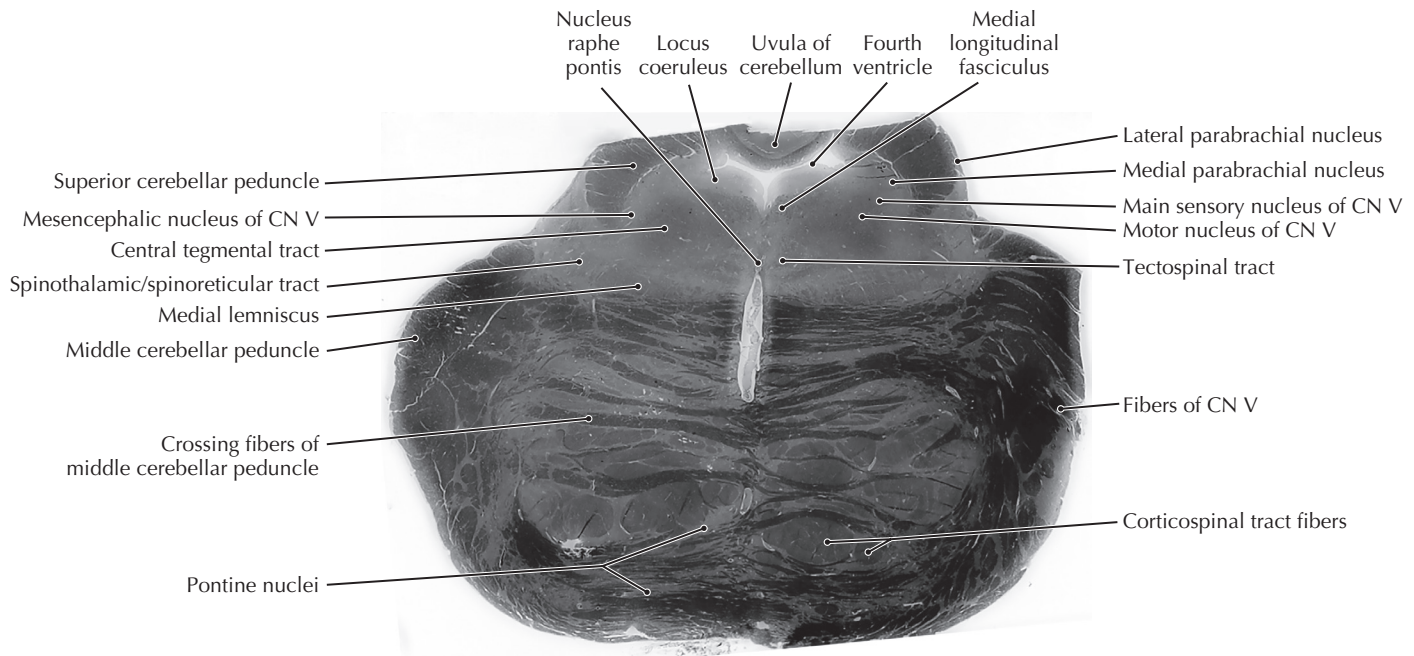
by UMN damage to the corticospinal and rubrospinal systems, thereby disinhibiting the lateral vestibular nuclei; (3) coma; (4) paralysis of ocular movements; and (5) small but reactive pupils. A pontine hemorrhage that results in coma is commonly lethal. A large infarct in the basilar artery may produce the same clinical picture. Some small, lacunar infarcts also may occur in the pons; these infarcts may produce purely motor symptoms (contralateral UMN paresis at base of pons), ataxia, or both (cerebellar peduncles, pontine nuclei).



## Pons–Level of Trigeminal Motor and Main Sensory Nuclei



Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



## 11.9 BRAIN STEM CROSS-SECTIONAL ANATOMY: SECTION 9

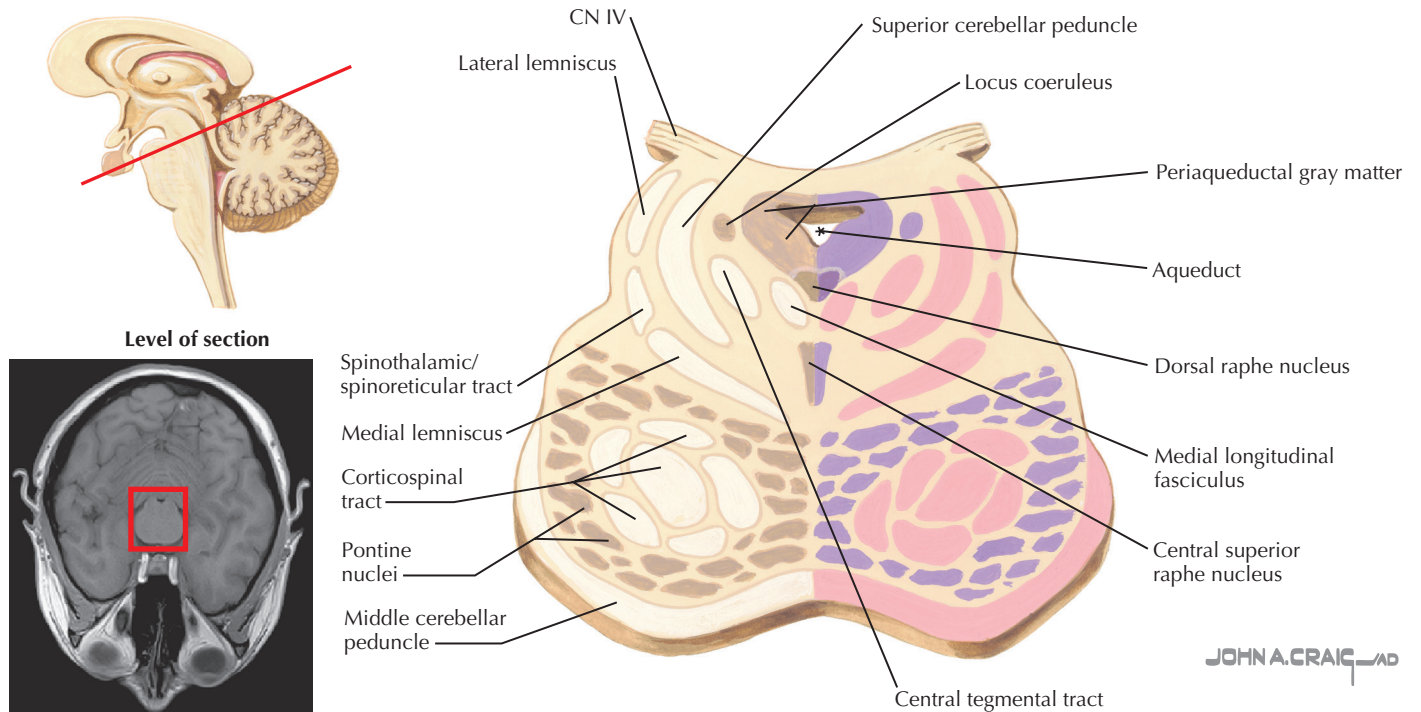
### CLINICAL POINT

A vascular lesion of circumferential branches of the basilar artery or the anterior inferior cerebellar artery can cause lateral pontine syndrome, which is characterized by (1) contralateral loss of sensation in the body, both epicritic and protopathic (medial lemniscus and anterolateral system); (2) loss of pain and temperature sensation on the contralateral face (ventral trigeminal lemniscus, located on dorsal surface of the medial lemniscus); (3) loss of fine, discriminative touch

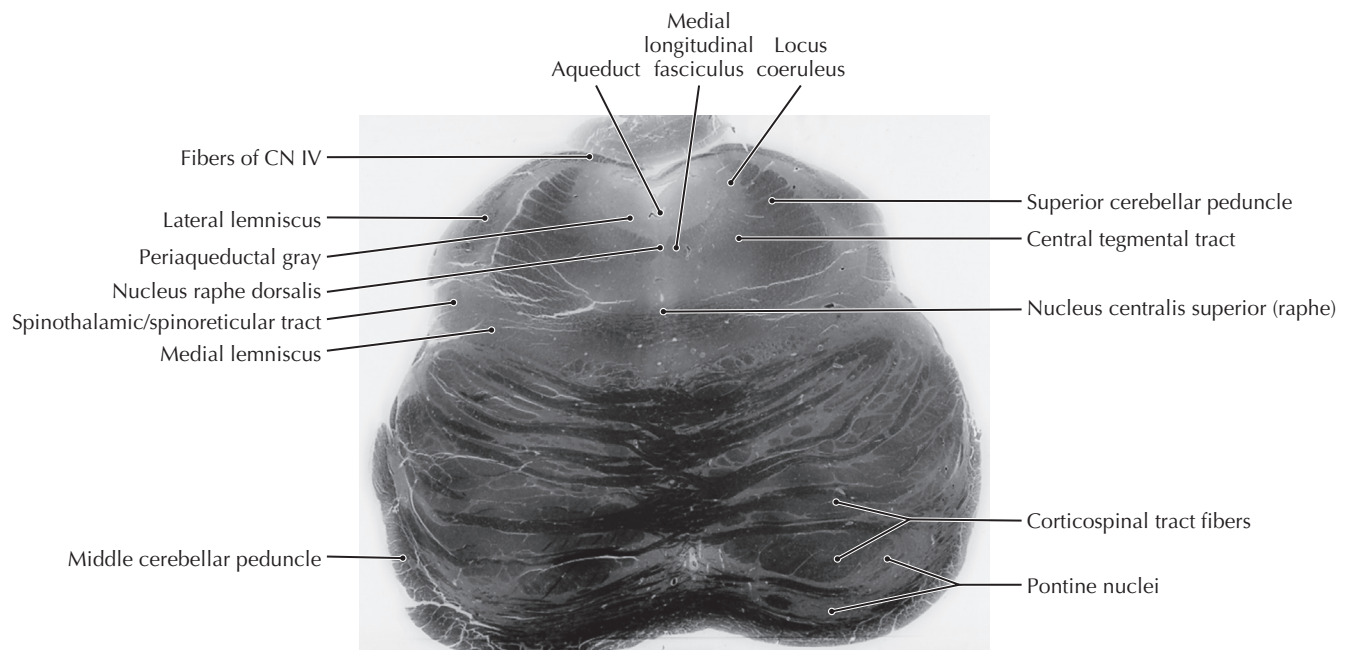
(main sensory nucleus of CN V) or impaired general sensation (CN V fibers) on the ipsilateral face; (4) ipsilateral paralysis of muscles of mastication (motor nucleus of CN V); (5) limb ataxia (middle and superior cerebellar peduncles); (6) paralysis of conjugate gaze to the ipsilateral side (parapontine reticular formation and its connections); and (7) other possible ipsilateral brain stem problems, depending on the extent of the vascular involvement, such as deafness or tinnitus (auditory nuclei or nerve fibers); vertigo and nystagmus (vestibular nuclei or nerve fibers); facial palsy (CN VII nucleus or nerve fibers); and Horner's syndrome (descending hypothalamo-spinal sympathetic connections).



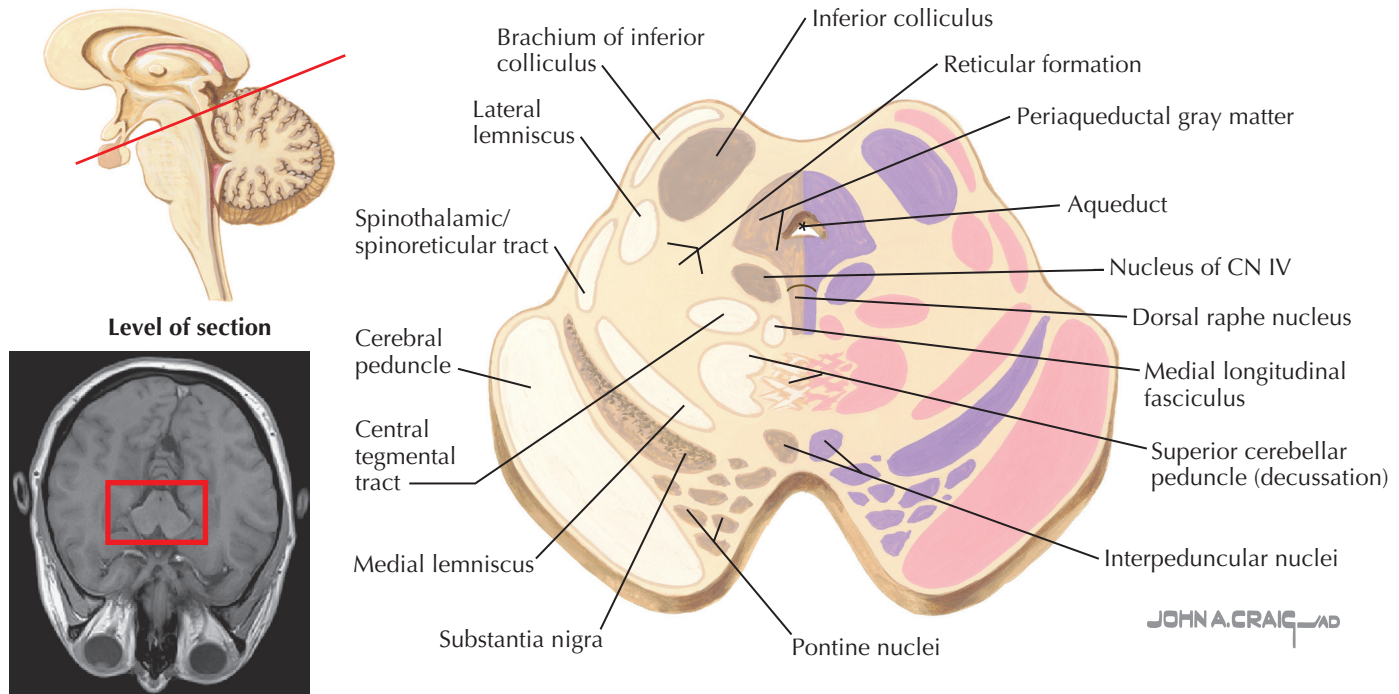
### Pons-Midbrain Junction–Level of CN IV and Locus Coeruleus



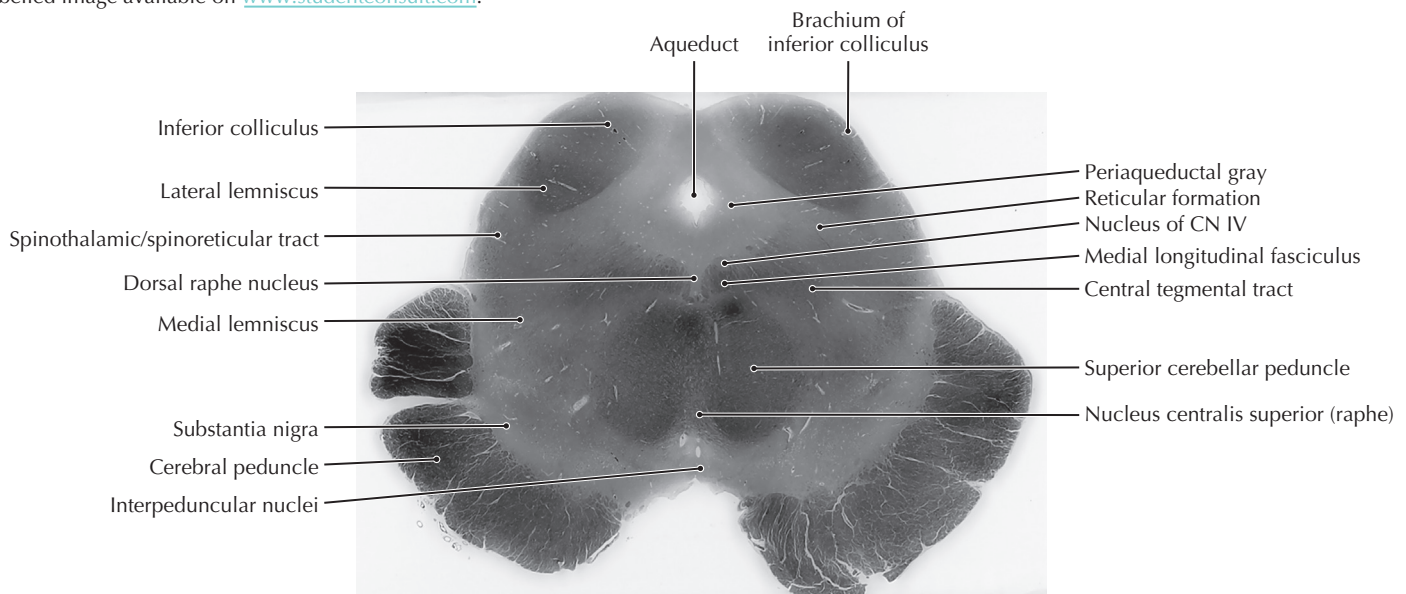
Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



## Midbrain–Level of the Inferior Colliculus



Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



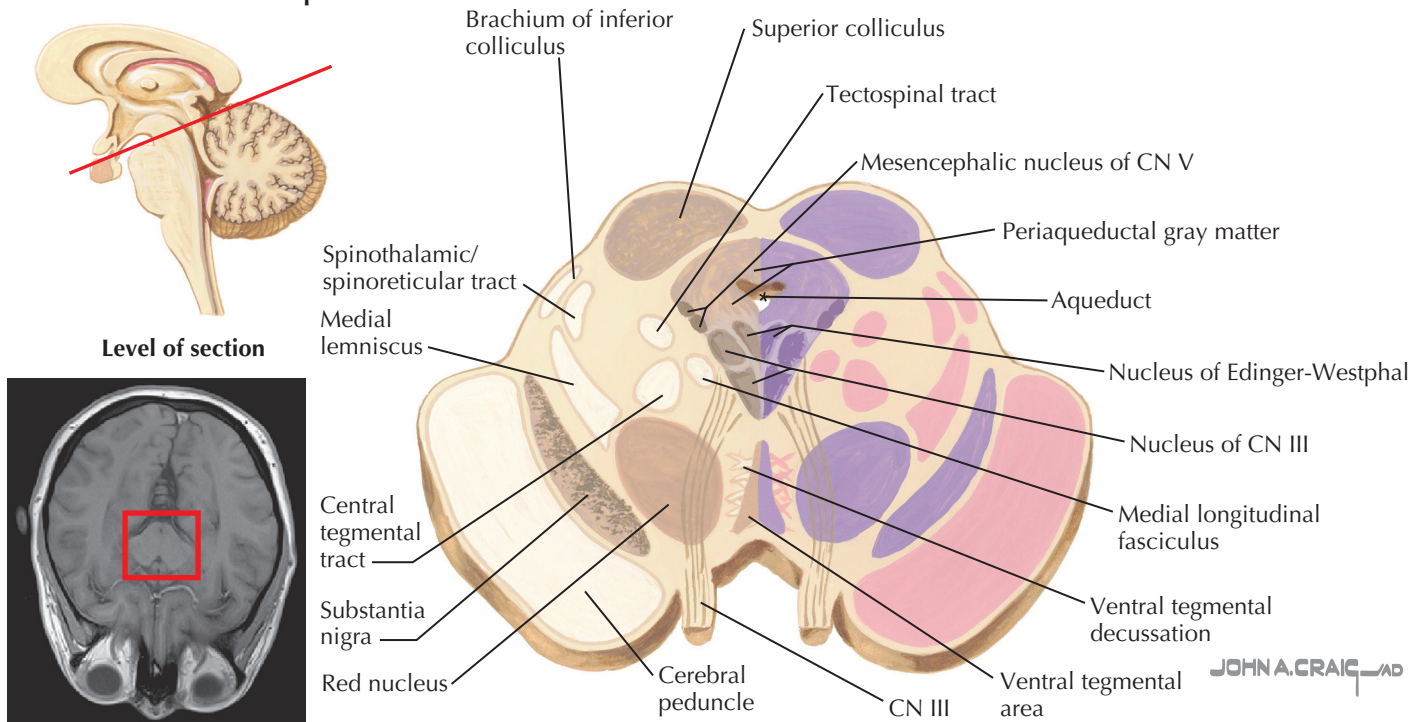
### 11.11 BRAIN STEM CROSS-SECTIONAL ANATOMY: SECTION 11

#### CLINICAL POINT

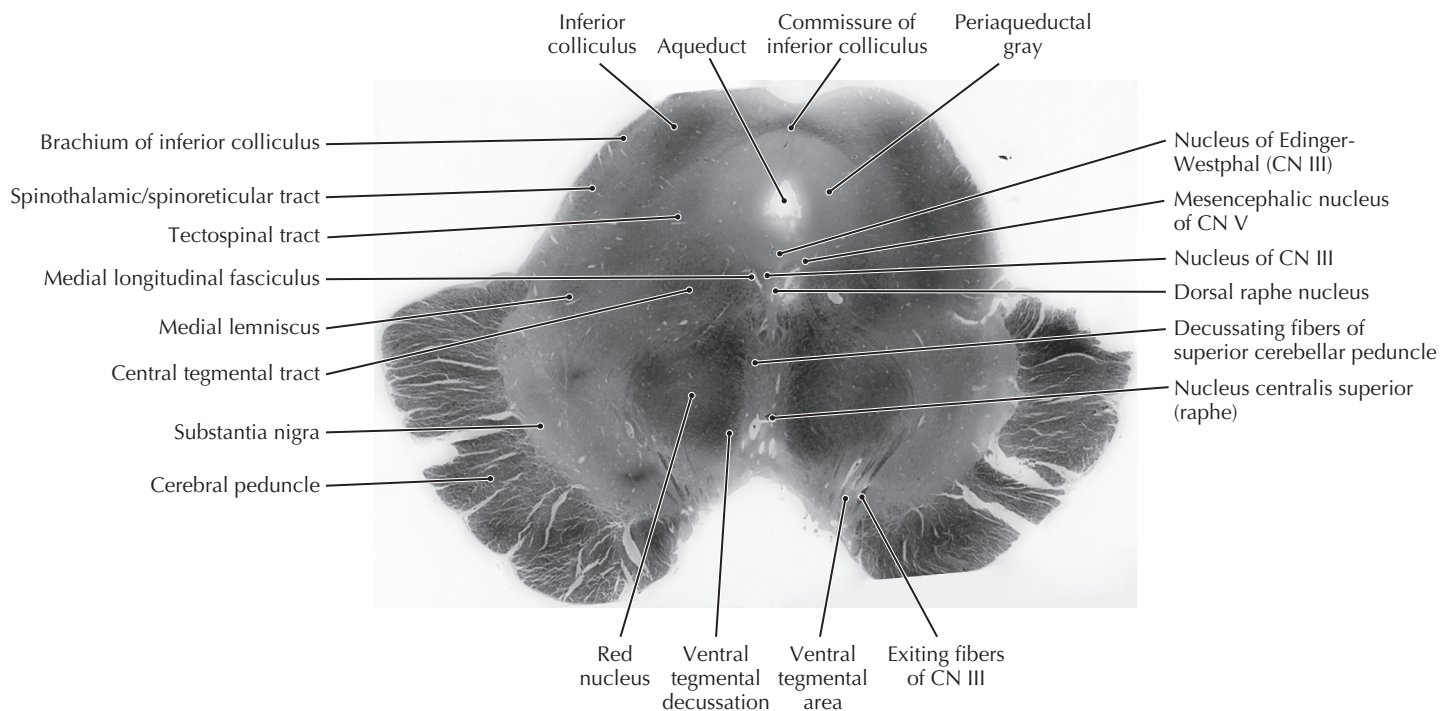
A space-occupying lesion in the forebrain, such as a bleed (epidural or subdural hematoma), a tumor, or increased intracranial pressure resulting from a variety of causes, can cause herniation of the forebrain through the tentorium cerebelli. This transtentorial herniation displaces the thalamus and upper midbrain in a downward direction and causes a variety of changes in brain function. These changes are characterized by functions attributable to the remaining intact lower midbrain and more caudal structures, with loss of function of the upper midbrain and more rostral structures. Most conspicuous is a progressive deterioration of the state of consciousness, rapidly going from drowsiness to stupor to an unarousable state of coma; conscious-

ness requires an intact brain stem reticular formation and at least one functioning cerebral hemisphere. When both hemispheres are non-functional, coma ensues. With the loss of activity in the corticospinal system and the rubrospinal system and removal of cortical influence on the other UMN pathways, a state of decerebration occurs (called decerebrate rigidity, although it is really spasticity, not true rigidity). The neck is extended (opisthotonus), the arms and legs are extended and rotated inward, and the hands, fingers, feet, and toes are flexed. Plantar responses are extensor. Cheyne-Stokes respiration is seen (crescendo-decrescendo breathing), followed at a slightly later stage of damage by shallow hyperventilation. The pupils are midsized and usually unresponsive because of compression of the third nerves against the free edge of the tentorium. Caloric testing or the doll's-eye maneuver shows no vertical eye movements (visual tectal damage), and the eyes do not move in a conjugate fashion.

## Midbrain–Level of the Superior Colliculus

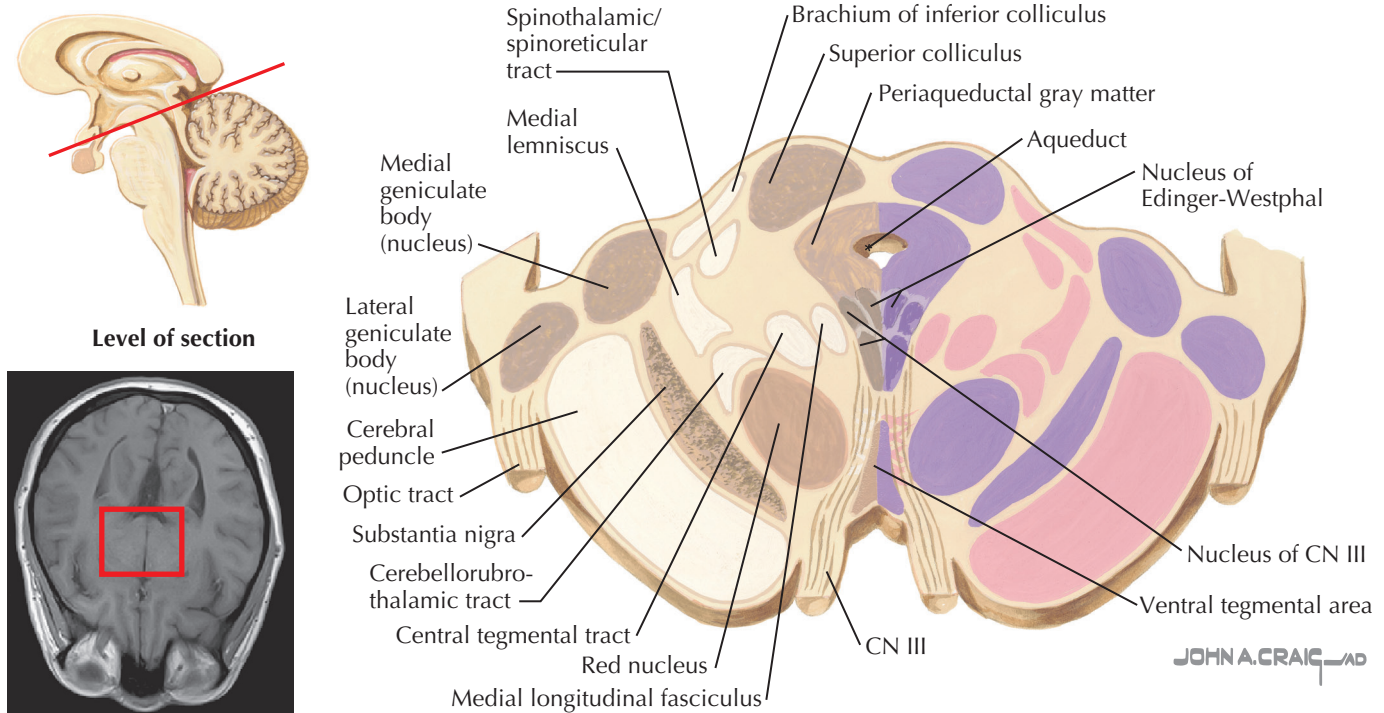


Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).

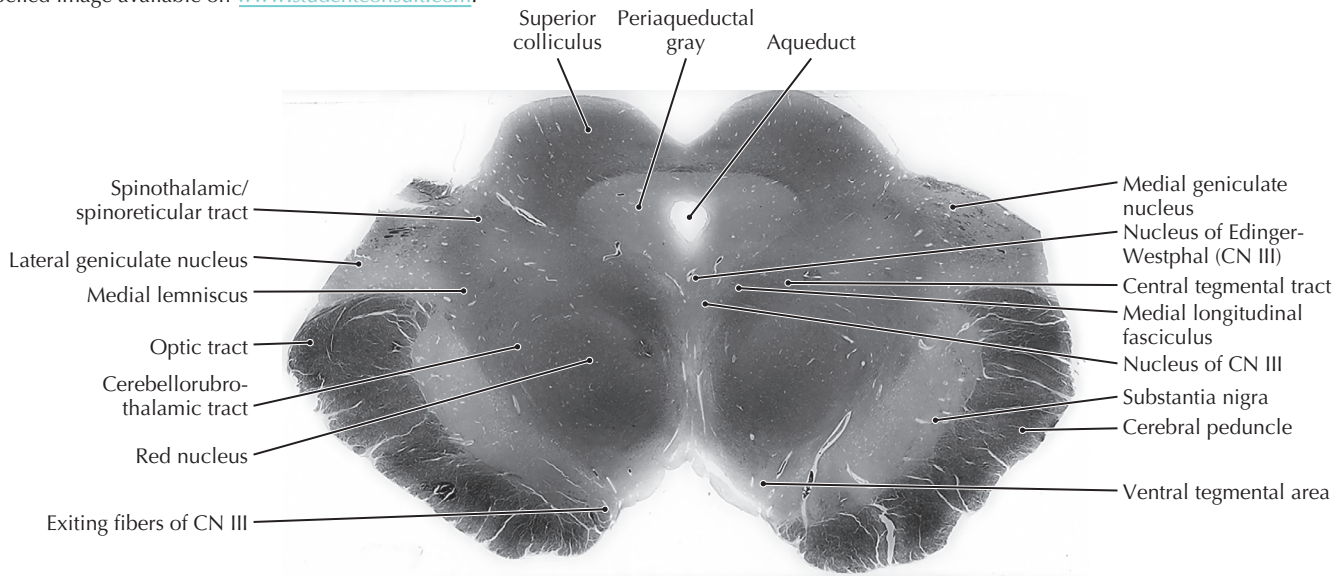




## Midbrain–Level of the Medial Geniculate Body



Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



### 11.13 BRAIN STEM CROSS-SECTIONAL ANATOMY: SECTION 13

#### CLINICAL POINT

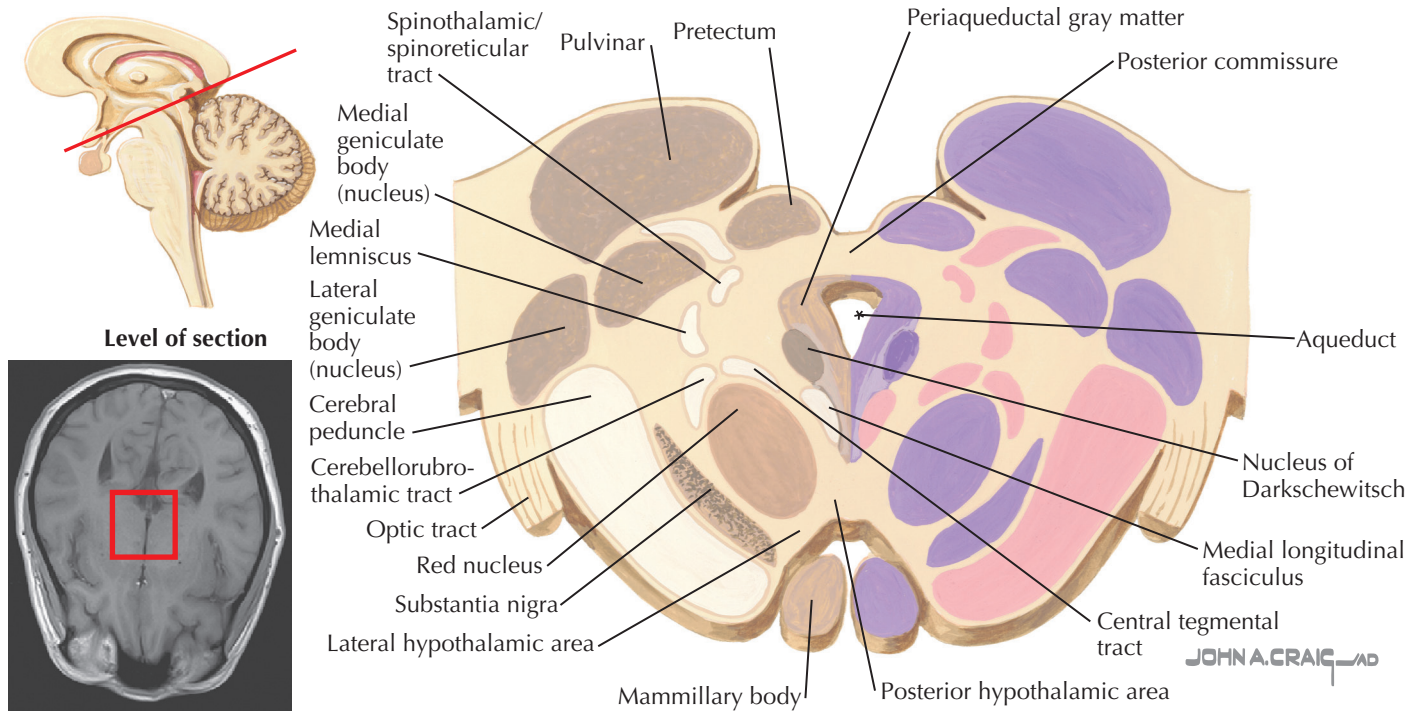
Paramedian regions of the upper midbrain receive their blood supply mainly from branches of the posterior cerebral and posterior communicating arteries. A vascular lesion at this level (Weber's syndrome) results in damage to the exiting third nerve fibers, the medial and central portions of the cerebral peduncle, and some passing tracts.

A supratentorial mass lesion also can cause lateral and downward compression of one cerebral peduncle and the third nerve against the free edge of the tentorium cerebelli, presenting a similar clinical picture. Compression of the cerebral peduncle with possible involvement of the red nucleus on the affected side produces contralateral

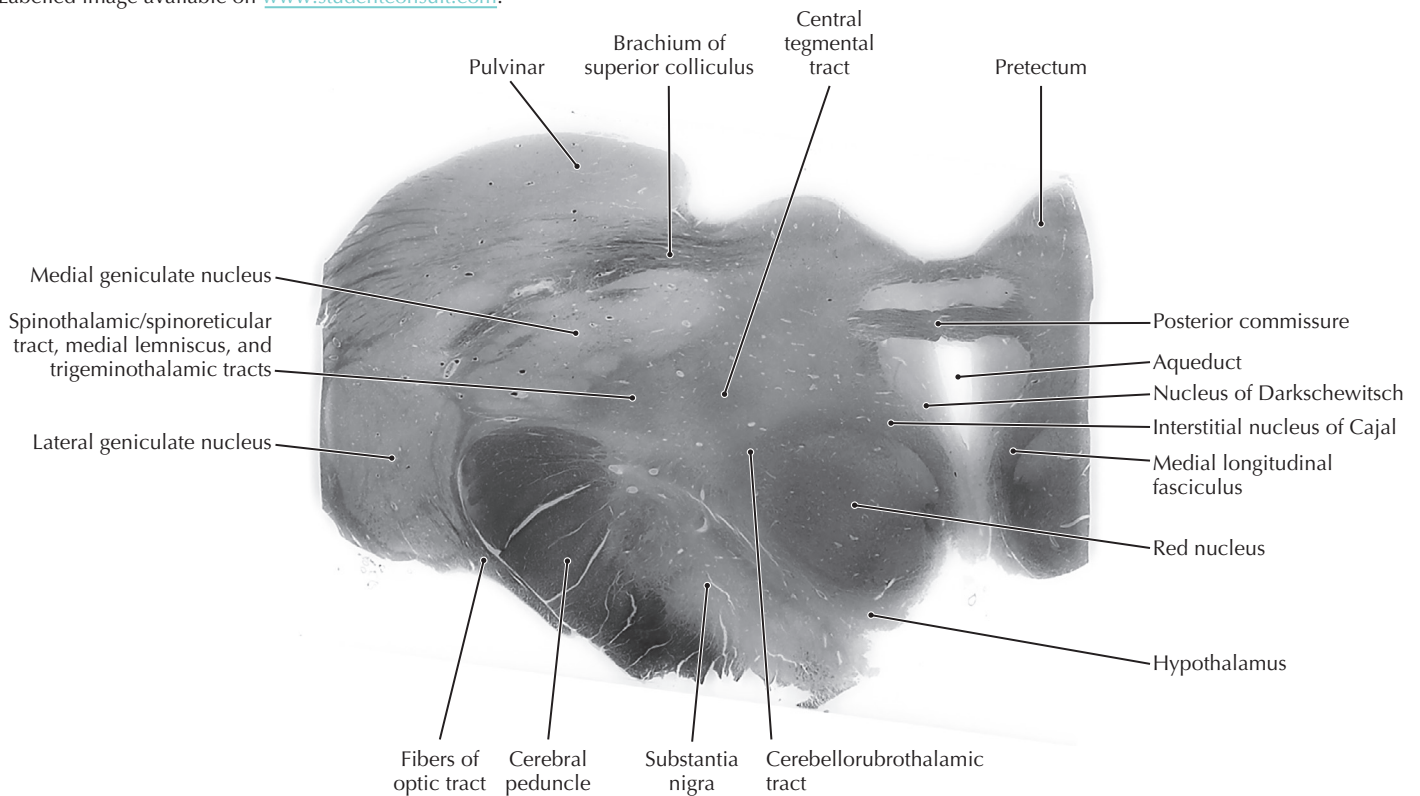
hemiplegia, rapidly evolving to a spastic state with a plantar extensor response.

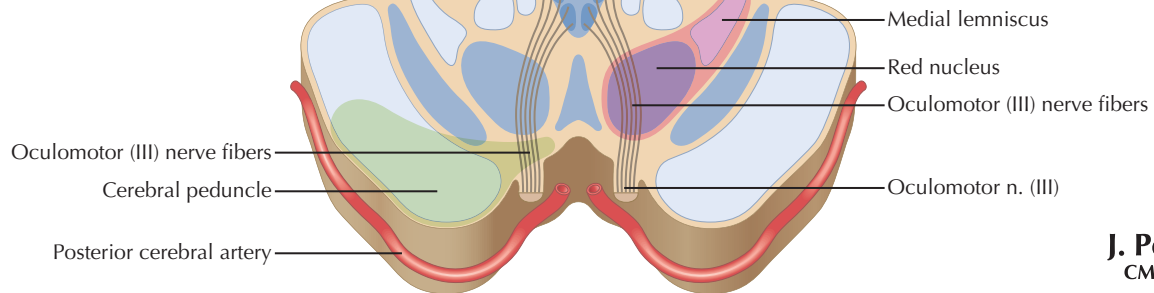
A central (lower) facial palsy occurs because of damage to corticobulbar fibers, which travel in the cerebral peduncle. An ipsilateral oculomotor palsy also occurs, with the ipsilateral eye deviated laterally and the ipsilateral pupil fixed (unresponsive to light) and dilated because of unopposed actions of the sympathetics. If the lesion involves the substantia nigra, red nucleus, pallidothalamic fibers, or dentatorubral and dentatothalamic fibers, contralateral movement problems may occur, including akinesia, intention tremor, or choreoathetoid movements. Damage to these later structures, with their accompanying contralateral problems, may occur in isolation along with third-nerve damage caused by more distal vascular involvement of the paramedian branches to the upper midbrain (Benedict's syndrome).

### Midbrain-Diencephalon Junction–Level of the Posterior Commissure

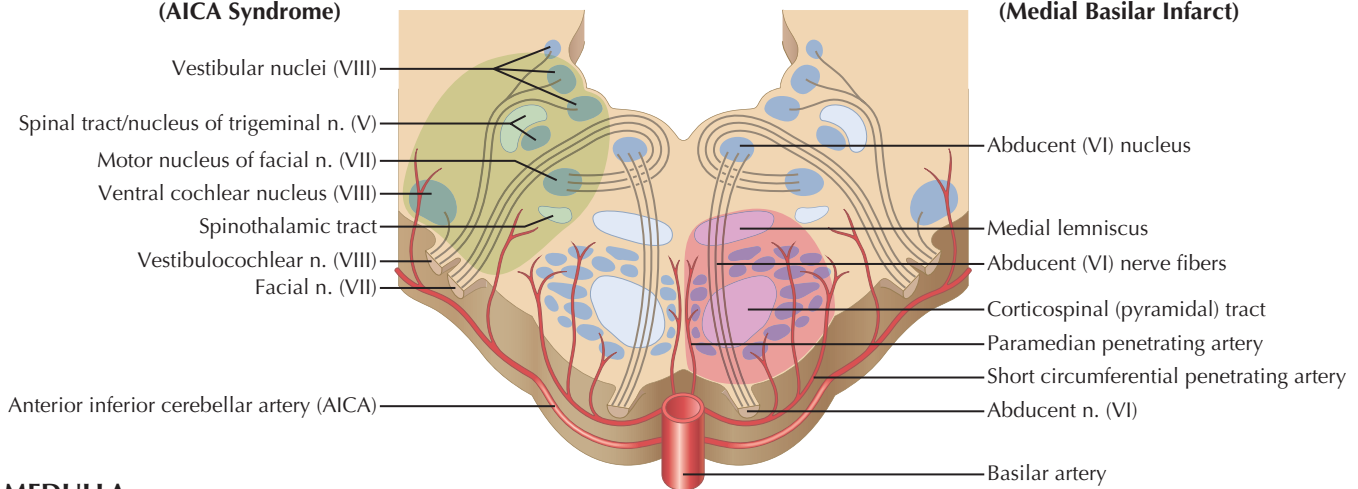
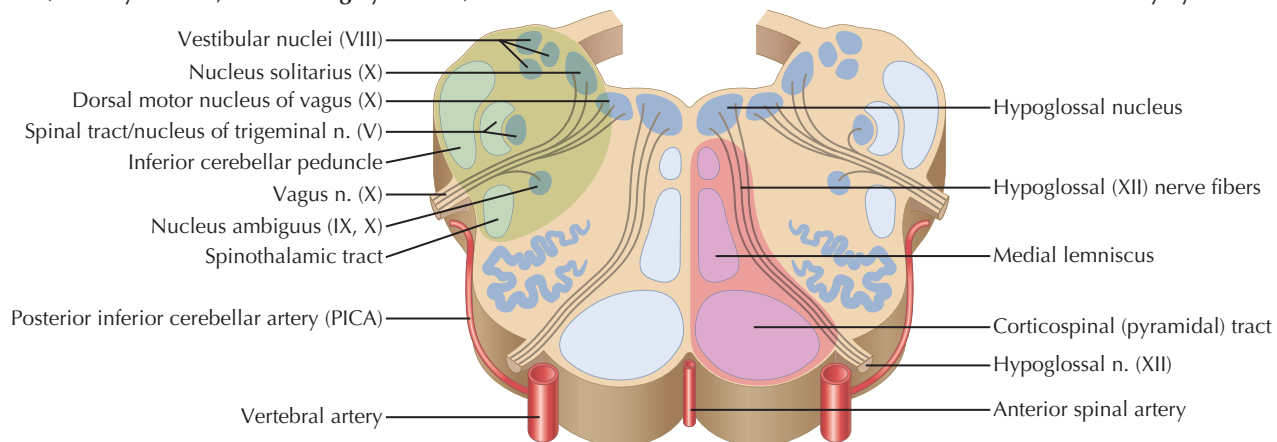


Labelled image available on [www.studentconsult.com](http://www.studentconsult.com).



**MIDBRAIN****Medial Midbrain Syndrome  
(Weber Syndrome)****Paramedian Midbrain Syndrome  
(Benedikt Syndrome)**

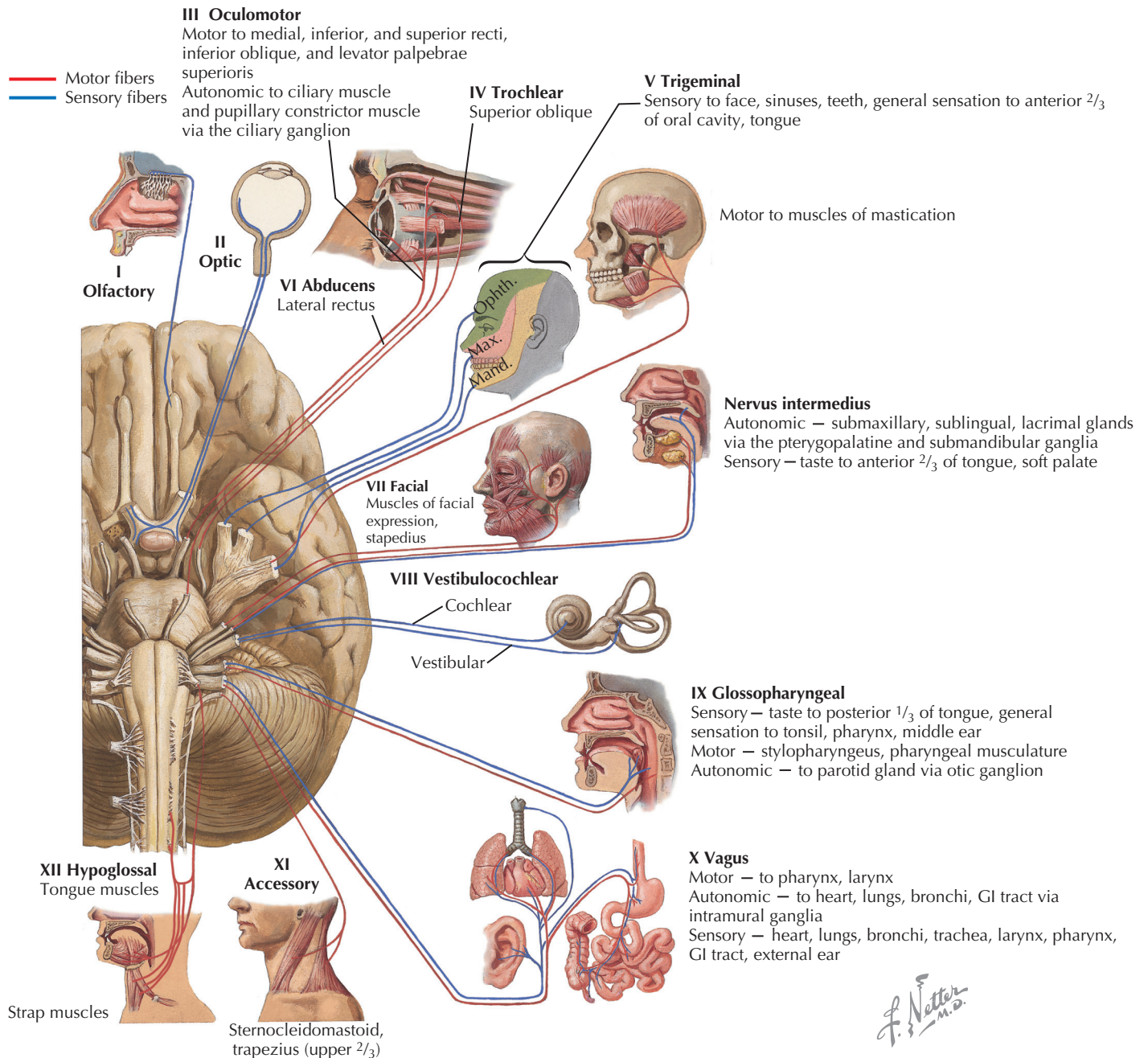
**J. Perkins**  
CMI, FAMI

**PONS****Lateral Pontine Syndrome  
(AICA Syndrome)****Medial Pontine Syndrome  
(Medial Basilar Infarct)****MEDULLA****Lateral Medullary Syndrome  
(PICA Syndrome; Wallenberg Syndrome)****Medial Medullary Syndrome****11.15 BRAIN STEM ARTERIAL SYNDROMES**

These brain stem cross sections demonstrate major regions of vascular infarcts affecting the medulla, pons, and midbrain. Thorough knowledge of the nuclei and tracts in each territory is necessary to understand the resultant symptoms. In the medulla the main syndromes are lateral medullary syndrome

(see [Plate 11.4 Clinical Point](#)) and medial medullary syndrome (see [Plate 4.2 Clinical Point](#)). In the pons the main syndromes are lateral pontine syndrome (see [Plate 11.9 Clinical Point](#)) and medial pontine syndrome (see [Plate 11.6](#)). In the midbrain the main syndromes are Weber's syndrome and Benedikt's syndrome (see [Plate 11.13 Clinical Point](#)).





## CRANIAL NERVES AND CRANIAL NERVE NUCLEI

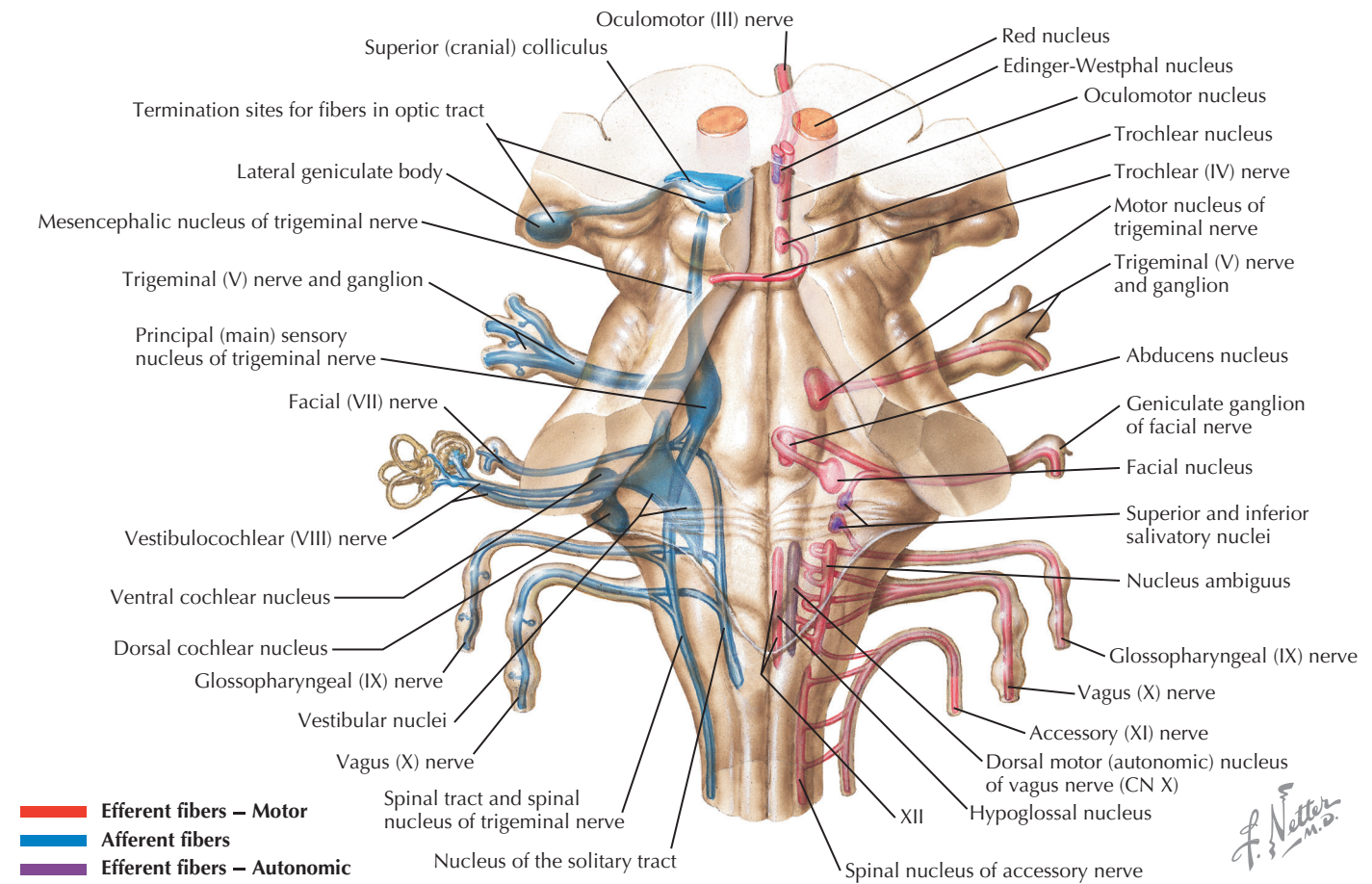
### 11.16 CRANIAL NERVES: SCHEMATIC OF DISTRIBUTION OF SENSORY, MOTOR, AND AUTONOMIC FIBERS

CNs I and II, both sensory, are tracts of the central nervous system (CNS) that are derived from the neural tube and myelinated by oligodendroglia. Cns III–XII emerge from the brain stem and supply sensory (Cns V, VII–X); motor (Cns III–VII and IX–XII); and autonomic (Cns III, VII, IX, X) nerve fibers to structures in the head, neck, and body (autonomic). All of the Cns that emerge from the brain stem distribute ipsilaterally to their target structures. With the exception of CN nucleus IV (trochlear) and some motor components of CN nucleus III (oculomotor), the CN nuclei are located ipsilateral to the point of emergence of the CN. The spinal accessory portion of CN XI emerges from motor

neurons in the rostral spinal cord; it ascends through the foramen magnum and then exits with Cns IX and X; thus it is considered a CN.

#### CLINICAL POINT

Multiple Cns can be affected by some pathological conditions, such as tumors and granulomas, brain stem infarcts, leptomeningeal carcinomatosis, and aneurysms. Extramedullary pathology affects mainly the sensory, motor, and autonomic components of the involved Cns: internal pathology in the brain stem also involves the long tracts. An aneurysm in the cavernous sinus may involve Cns III–VI. A large tumor in the middle cranial fossa in the retrosphenoid space may affect cranial nerves III–VI. A large tumor in the cerebellopontine angle involves Cns VII and VIII and sometimes expands to involve V and IX. Tumors and aneurysms in the jugular foramen may involve Cns IX, X, and XI. Granulomatous lesions such as sarcoids in the posterior retroparotid space may affect cranial nerves IX–XII as well as the sympathetic nerves to the head.



**Cranial Nerves and Their Nuclei: Schematic View From Above**

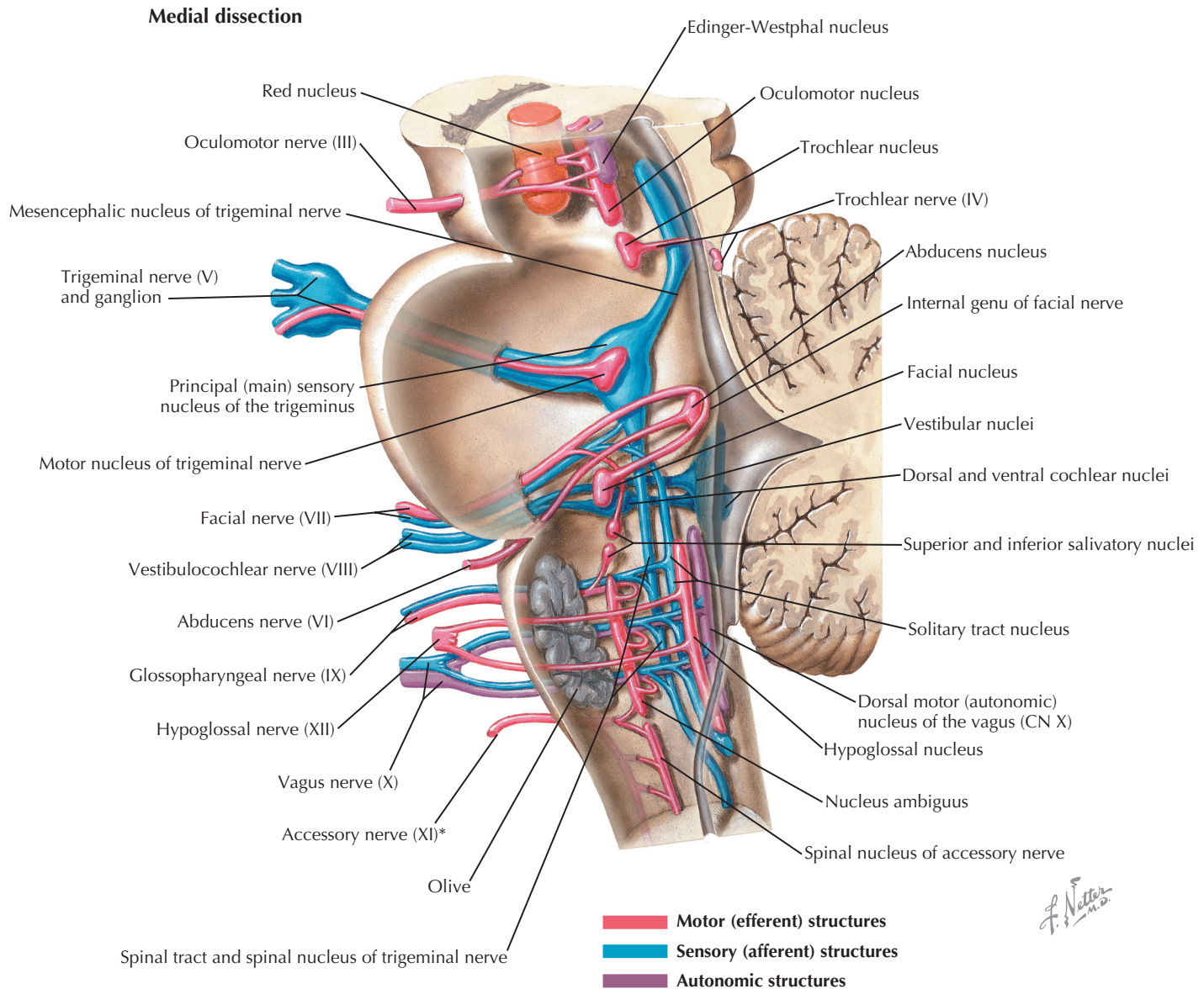
### 11.17 CRANIAL NERVES AND THEIR NUCLEI: SCHEMATIC VIEW FROM ABOVE

The LMNs of the brain stem are localized in a medial column (CN motor nuclei for III [oculomotor]; IV [trochlear]; VI [abducens]; and XII [hypoglossal]) and a lateral column (CN motor nuclei for V [trigeminal]; VII [facial]; IX and X [ambiguous]; and XI [spinal accessory]). Preganglionic parasympathetic nuclei are found medially in the Edinger-Westphal nucleus (CN III) and the dorsal (motor) vagal nucleus (CN X) and laterally in the superior (CN VII) and inferior (CN IX) salivatory nuclei. Secondary sensory nuclei include the main sensory and descending nuclei of CN V, the vestibular nuclei and cochlear nuclei (CN VIII), and the nucleus solitarius (CNs VII, IX, and X). The superior colliculus and the lateral geniculate body (nucleus) receive secondary sensory axonal projections from the optic tract; the inferior colliculus receives input from the cochlear nuclei and other accessory auditory nuclei. The nuclei gracilis and cuneatus, located in the medulla, receive input from dorsal root ganglion cells, which convey epicritic somatosensory modalities (fine, discriminative touch, vibratory sensation, joint position sense).

#### CLINICAL POINT

CNs I, II, V, and VII–X have primary afferent components. CN I, the olfactory nerve, is a CNS tract and terminates directly in limbic fore-brain structures, unlike any other CNs. CN II, the optic nerve, also is a CNS tract; its retinal ganglion cells act as a secondary sensory nucleus, projecting to the thalamus (lateral geniculate body), superior colliculus, pretectum, suprachiasmatic nucleus of the hypothalamus, and other brain stem sites. CNs V and VII–X can be affected by peripheral nerve problems, such as demyelinating disease (Guillain-Barré syndrome), neuropathies (diabetic), tumors, vascular infarcts, traumas, and other pathology; these nerve problems generally result in loss of the specific sensory modality carried by that nerve. Secondary sensory CN nuclei associated with the peripheral CNs (III–XII) include the trigeminal nuclei (main sensory, descending [spinal] nucleus), nucleus solitarius, cochlear nuclei (dorsal and ventral), and vestibular nuclei (medial, lateral, inferior, superior). These nuclei can be damaged by vascular infarcts, tumors, and other pathology; such pathology often involves other central nuclei and long tracts and produces syndromes that clearly indicate CNS pathology (e.g., UMN damage). Involvement of some secondary sensory cranial nerve nuclei (e.g., the descending nucleus of CN V damaged by a posterior inferior cerebellar artery infarct) results in a dissociated loss of a specific set of modalities (pain and temperature) in the innervated territory (ipsilateral face); a trigeminal nerve lesion on one side results in total anesthesia in the innervated territory.





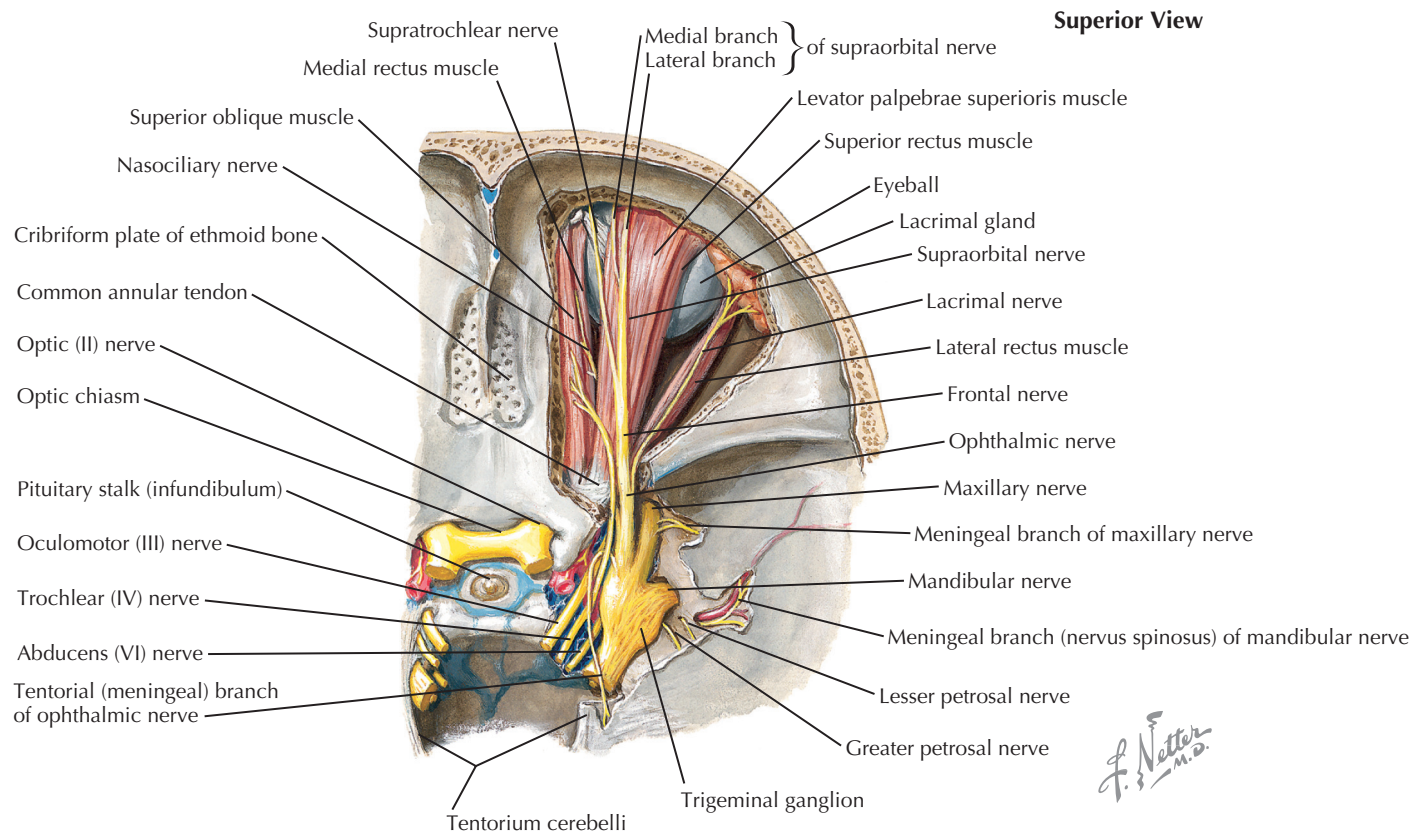
### 11.18 CRANIAL NERVES AND THEIR NUCLEI: SCHEMATIC LATERAL VIEW

CN III exits from the ventral and medial surface of the midbrain. CN IV is the only CN to exit from the dorsal surface of the brain stem, in the midbrain near the pons-midbrain junction. CN V exits from the lateral surface of the mid pons. CN VI exits from the pons medially, just rostral to the medullo- pontine junction. CNs VII and VIII exit from the cerebello- pontine angle at the junction of the medulla and pons. CNs IX and X exit from the lateral part of the medulla and are joined by CN XI, which ascends through the foramen magnum. CN XII exits medially from the preolivary sulcus. These CN sites of entry and exit are important localizing features in the brain stem that permit regional localization of lesions result- ing from vascular insults, tumors, and degenerative disorders.

#### CLINICAL POINT

The CN nuclei that contain LMNs are found in two longitudinal columns, including a medial column (CN nuclei III, IV, VI, and XII)

and a lateral column (motor CN nuclei V, VII, and nucleus ambiguus). These LMN groups are found in the CNS and send axons into the peripheral nervous system to synapse on their appropriate groups of skeletal muscles using acetylcholine, and they exert important trophic influences on their innervated muscles. An LMN lesion (bulbar polio, amyotrophic lateral sclerosis, and other LMN palsies) results in total paralysis of the affected muscle; atrophy is caused by denervation, loss of tone, and loss of reflexes. Denervated muscles commonly demon- strate denervation hypersensitivity, with resultant fibrillation as seen on an electromyogram. As LMNs die (particularly conspicuous in amyotrophic lateral sclerosis) their agonal electrical responses occur as spontaneous discharges of individual motor units (an LMN and its innervated muscle fibers); each discharge produces a visible fascicula- tion (or twitch). With some LMN disorders such as polio, if enough neighboring LMNs survive, their axons can sprout and reinnervate previously denervated skeletal muscle fibers; this process must occur within approximately 1 year, or the atrophy becomes permanent. In UMN paralysis, in which the LMNs do not die, the affected muscle fibers are not denervated; reflexes are brisk, tone is increased with passive stretch (spasticity), and pathological reflexes (plantar extensor response) are seen.



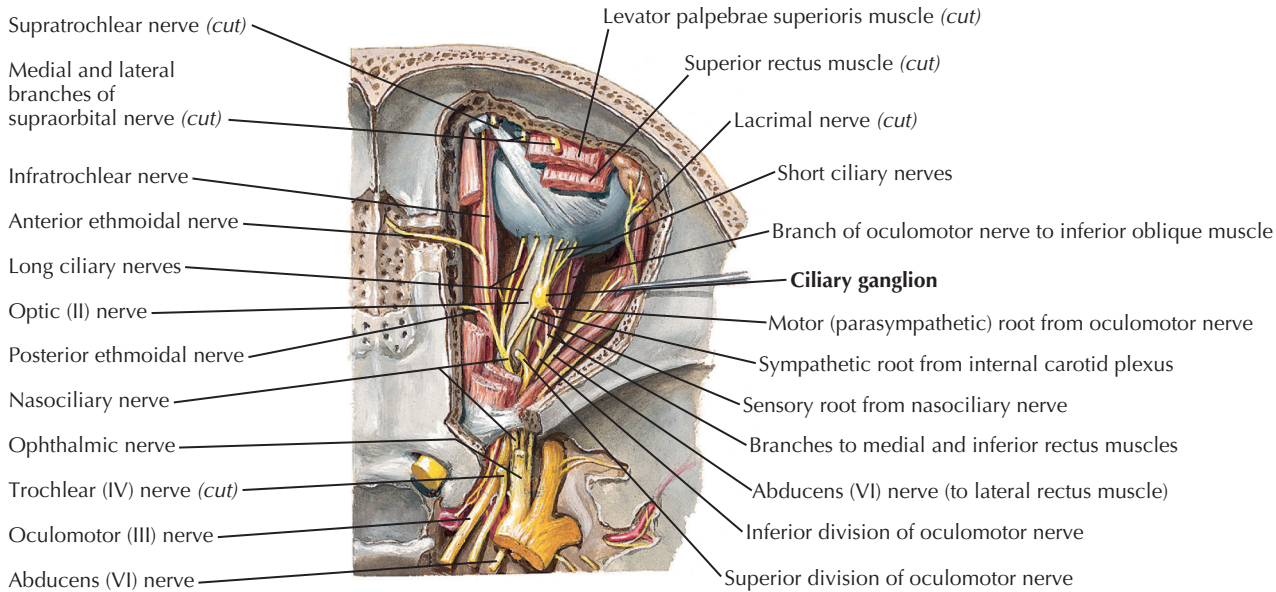
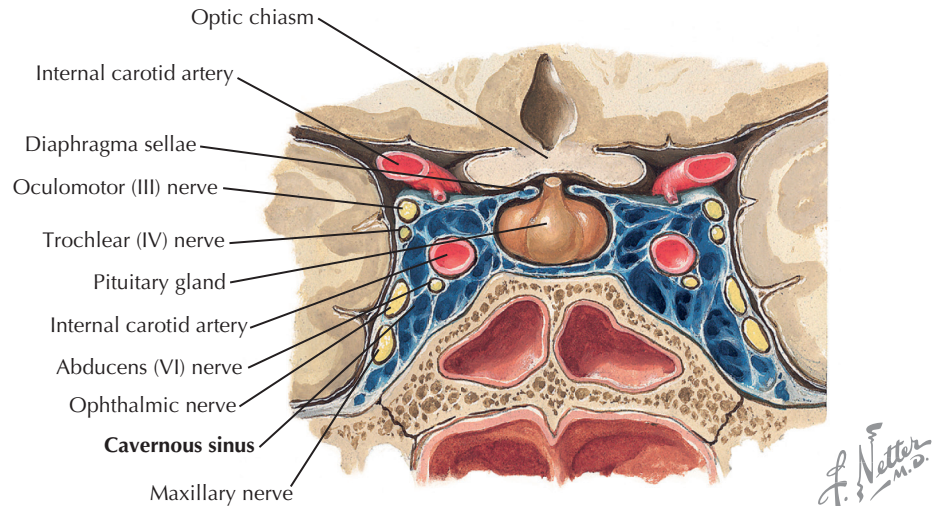
### 11.19 NERVES OF THE ORBIT

CN II carries visual information from the ipsilateral retina. Axons from the temporal hemiretinas remain ipsilateral, whereas axons from the nasal hemiretinas cross the midline in the optic chiasm. All axons then enter the optic tract. CNs III (from oculomotor nuclei), IV, and VI innervate the extrinsic muscles of the eye. Sensory portions of the ophthalmic division of V supply general sensation to the cornea and eyeball and provide the afferent limb of the corneal reflex. Motor fibers of CN VII innervate the orbicularis oculi muscle, closing the eye; these fibers constitute the efferent limb of the corneal reflex.

#### CLINICAL POINT

CN II (the optic nerve) is a CNS tract myelinated by oligodendroglia. It can be damaged by demyelinating disease (optic neuritis in multiple sclerosis), by optic nerve gliomas, by ischemic injury (central retinal artery), or by trauma (sphenoid fracture). The resultant defect is ipsilateral blindness or a scotoma (blind spot). The ipsilateral nature of the deficit rules out optic chiasm, optic tract, or central visual lesions. The retina also is CNS tissue and can undergo neurodegenerative changes. Macular degeneration involves damage to the cone-intensive regions of the retina (macula) and leads to the inability to read and the loss of acuity. Increased intracranial pressure can result in papilledema, a condition in which pressure pushes the optic nerve head inward (toward the center of the eyeball), producing a swollen appearance on ophthalmoscopy. This process takes 24 hours to occur after onset of intracranial pressure; the presence of papilledema is used diagnostically to identify increased intracranial pressure.



**A. Superior view with extraocular muscles partially cut away****B. Coronal section through the cavernous sinus****11.20 NERVES OF THE ORBIT (CONTINUED)**

Parasympathetic preganglionic fibers from the nucleus of Edinger-Westphal distribute to the ciliary ganglion, which supplies the pupillary constrictor muscle and the ciliary muscle (accommodation for near vision). Preganglionic parasympathetic axons from the superior salivatory nucleus distribute to the pterygopalatine ganglion, which supplies the lacrimal gland (tear production). Sympathetic postganglionic nerve fibers from the superior cervical ganglion supply the pupillary dilator muscle and the superior tarsal muscle (damage results in mild ptosis). CNs III, IV, VI, and V (ophthalmic and maxillary divisions) traverse the cavernous sinus and are vulnerable to damage by cavernous sinus thrombosis.

**CLINICAL POINT**

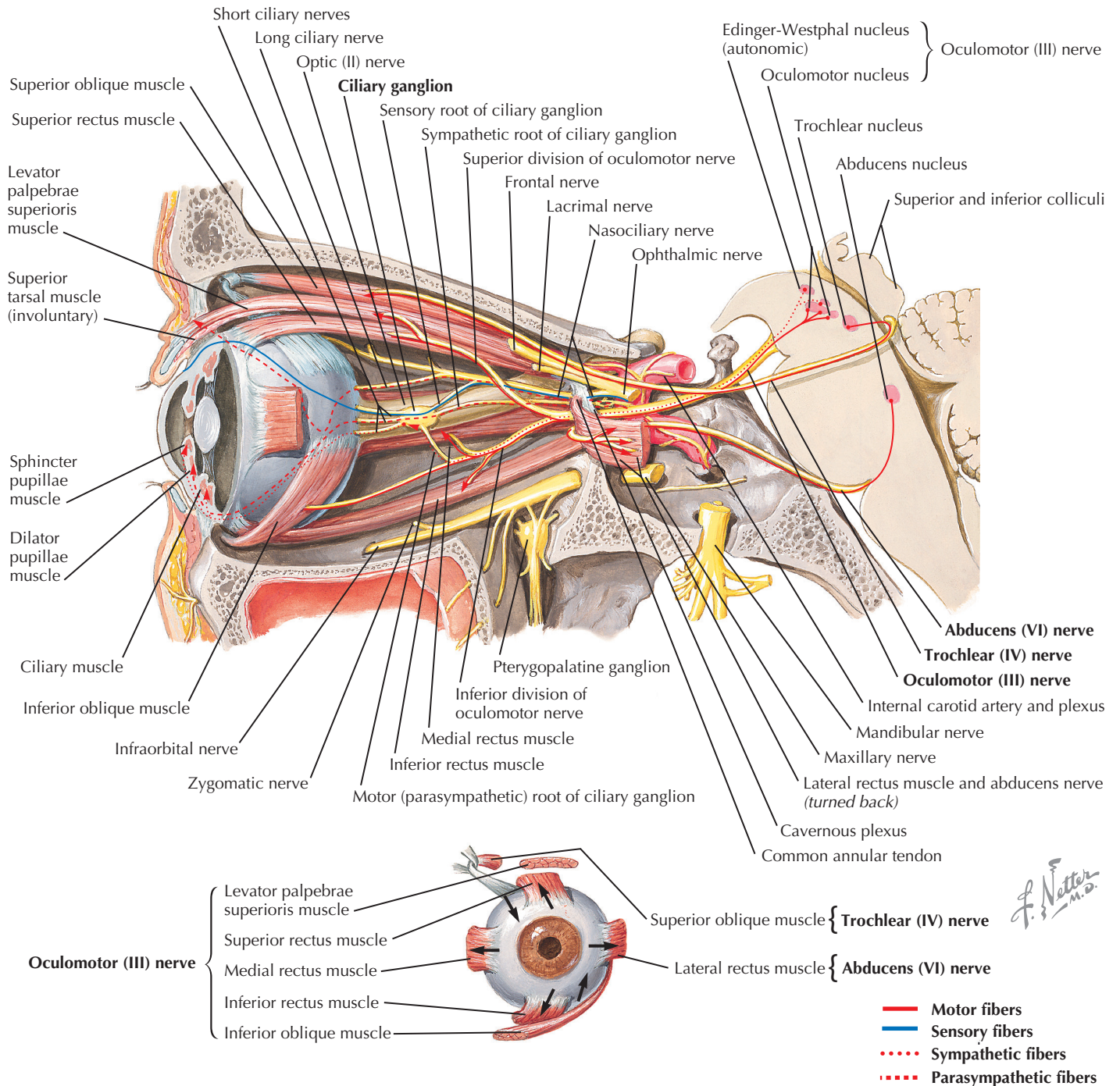
The extraocular nerves can be damaged by trauma, vascular infarcts, tumors, aneurysms, pressure (compression of CN III against the free

edge of the tentorium with transtentorial herniation), or other pathology. Oculomotor palsy (CN III) results in paralysis or weakness of the medial rectus, superior and inferior rectus, inferior oblique, and levator palpebrae superioris muscles. The most conspicuous deficit is the inability to adduct the ipsilateral eye, a lateral strabismus (resulting from unopposed action of the lateral rectus), and diplopia. Damage to the levator palpebrae superioris muscle results in profound ptosis of the ipsilateral eye. Lesions in CN III also disrupt the outflow from the Edinger-Westphal nucleus to the ciliary ganglion, producing a fixed (unresponsive) and dilated ipsilateral pupil.

A lesion in CN IV (trochlear) results in paralysis or weakness of the superior oblique muscle. This muscle is a depressor of the eye when it is directed nasally. Thus, a patient has difficulty walking down stairs and stepping off curbs and has trouble reading while lying down. The patient tries to compensate for a lesion in CN IV by turning the head away from the side of the lesion to avoid having to use the paralyzed muscle.

A lesion in CN VI (abducens) results in paralysis or weakness of the ipsilateral lateral rectus muscle, with a resultant medial strabismus and diplopia upon attempted lateral gaze.

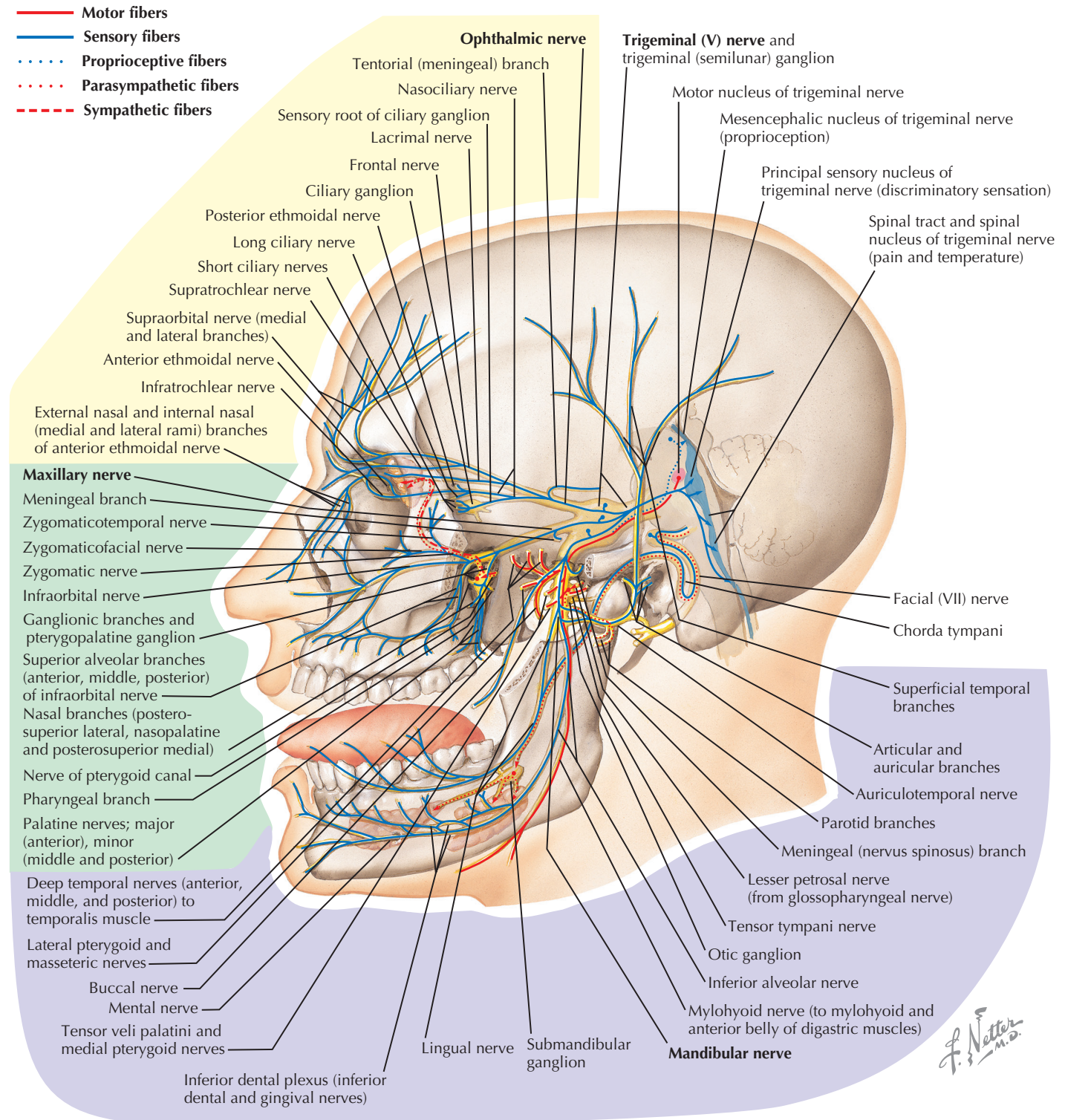




### 11.21 EXTRAOCULAR NERVES (III, IV, AND VI) AND THE CILIARY GANGLION: VIEW IN RELATION TO THE EYE

CN VI innervates the lateral rectus muscle; damage results in ipsilateral paralysis of lateral gaze. CN IV innervates the superior oblique muscle; damage results in inability to look in and down (most conspicuous when climbing stairs, stepping off a curb, reading in bed). CN III (oculomotor nuclei) innervates the medial rectus, superior rectus, inferior rectus, and inferior

oblique muscles (damage results in paralysis of the ipsilateral medial gaze) and also innervates the levator palpebrae superioris muscle (damage results in profound ptosis). The ciliary ganglion gives rise to postganglionic parasympathetic axons that supply the pupillary constrictor muscle and the ciliary muscle; damage results in a fixed and dilated pupil that does not constrict for the pupillary light reflex and does not accommodate to near vision.



Trigeminal Nerve (V)

### 11.22 TRIGEMINAL NERVE (V)

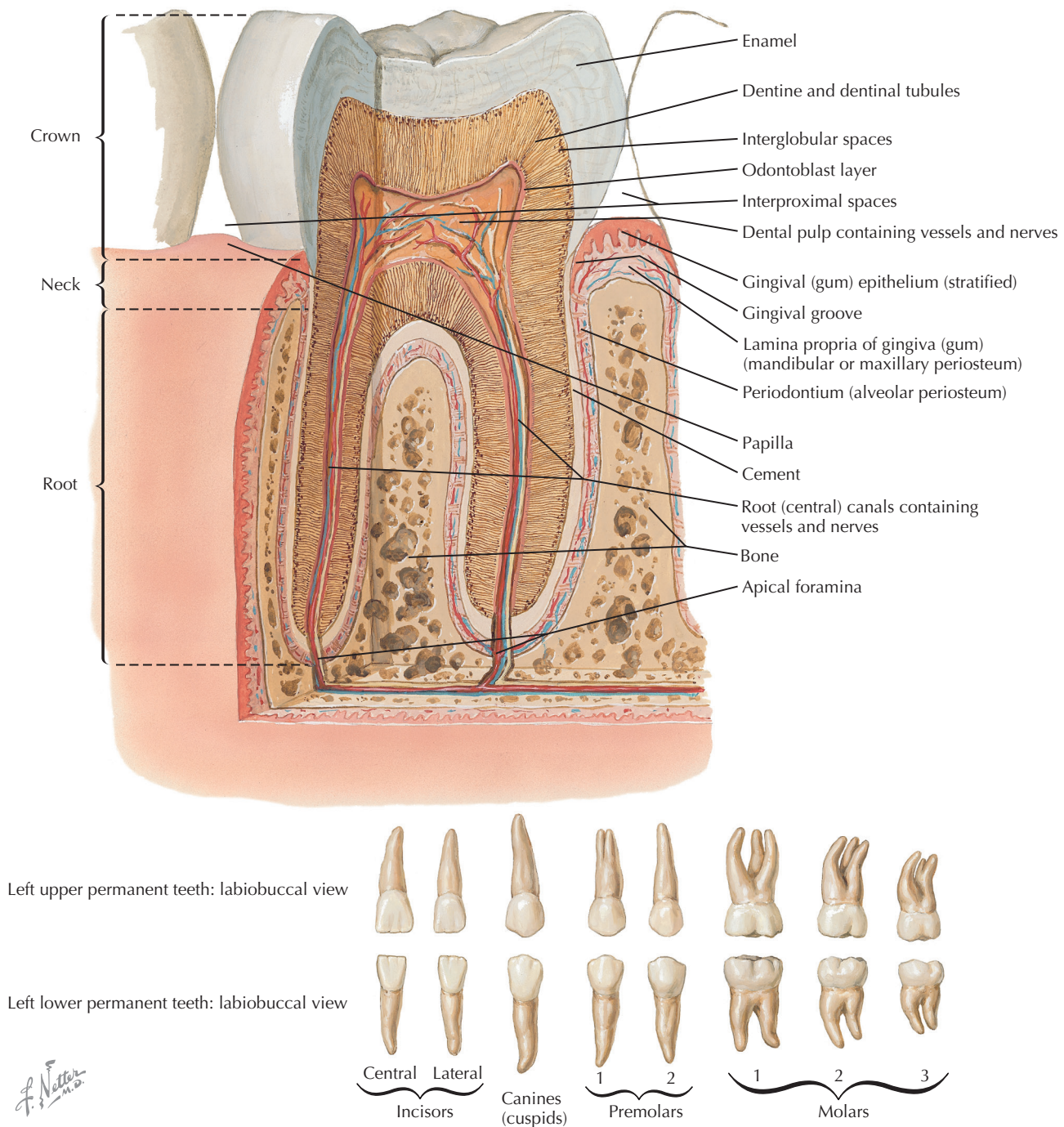
The trigeminal nerve (CN V) carries sensory information from the face, sinuses, teeth, and anterior portion of the oral cavity. It has three subdivisions: (1) ophthalmic—sensory innervation; (2) maxillary—sensory innervation; and (3) mandibular—sensory innervation and motor innervation of the masticatory muscles and tensor tympani muscles. Each of the subdivisions has a distinct distribution and sharp boundaries. Unlike the somatosensory dermatomes, which exhibit considerable overlap with nerve fibers of adjacent roots, the trigeminal subdivisions show no overlap at all. Damage to one of the subdivisions results in total anesthesia in the territory of sensory distribution.

Primary sensory axons from trigeminal (semilunar, gasserian) ganglion cells that process fine, discriminative touch (epicritic sensation) terminate in the main sensory nucleus of CN V and the rostral portion of the descending (spinal) nucleus of CN V. Axons that process pain and temperature sensation (protopathic sensation) terminate in the caudal and middle regions of the descending (spinal) nucleus of CN V. The trigeminal nerve also carries proprioceptive information from muscle spindles in muscles of mastication and extraocular muscles. Those primary sensory cell bodies are found in the mesencephalic nucleus of CN V within the CNS, the only example of primary sensory neurons residing in the CNS.

#### CLINICAL POINT

Trigeminal neuralgia (tic douloureux) involves sudden, brief (lasting less than a minute), excruciating paroxysms of pain, sometimes described as stabbing or lancinating, usually in the territory of one of the divisions of the trigeminal nerve. The maxillary and mandibular divisions are more common targets than the ophthalmic division, and the disorder is more common in older individuals. These episodes of pain may recur several times a day, with paroxysms experienced for weeks on end. Often there is a trigger point, at which mild stimuli such as light touch, chewing, or even talking can provoke an attack. During an attack, no loss of sensation occurs in the distribution of the affected branch. Trigeminal neuralgia can be idiopathic or symptomatic of other disorders. In some cases, compression of the trigeminal nerve root by a small aberrant branch of the superior cerebellar artery or another nearby artery is the suspected cause; in other cases a tumor, an inflammation, or a demyelinating plaque may precipitate such attacks. If trigeminal neuralgia occurs in the accompaniment of other progressive pathology, the neurological examination reveals sensory and motor deficits associated with the involved branch of the trigeminal nerve. Idiopathic trigeminal neuralgia usually can be treated with carbamazepine or other antiseizure and membrane-stabilizing agents, which sometimes permit the condition to regress. Surgical decompression of a compressing blood vessel may help. In other cases, the nerve root is ablated temporarily or permanently; the resultant functional deficit is often better tolerated than the excruciating paroxysms of pain.





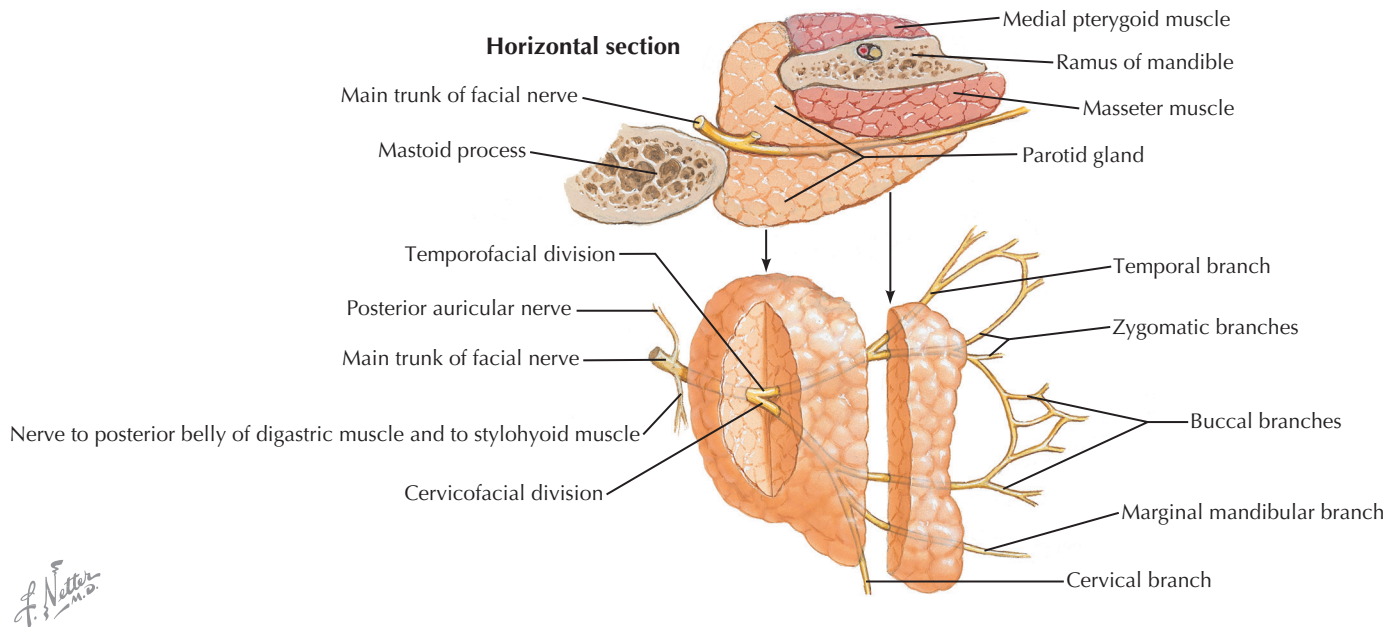
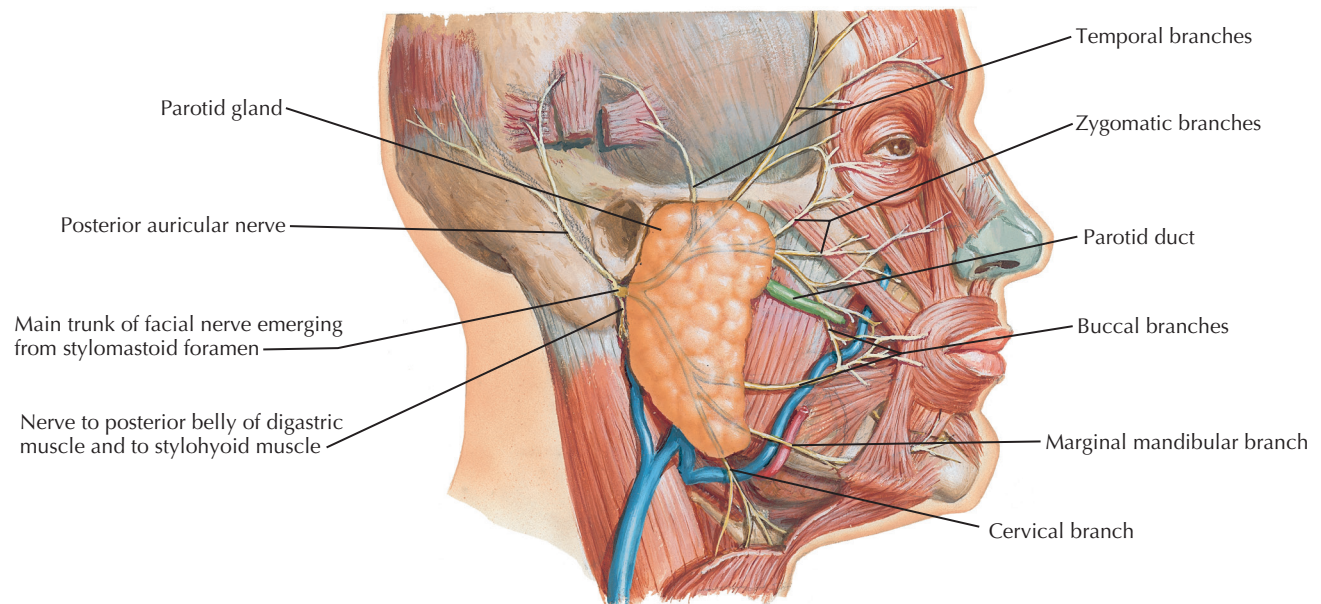
### 11.23 INNERVATION OF THE TEETH

Sensory nerve fibers of the maxillary (upper teeth) and mandibular (lower teeth) subdivisions of the trigeminal nerve innervate the dental pulp of the teeth. With erosion of a lesion

(decay) into the dental pulp or close to the dental pulp, these nerve fibers may become exquisitely sensitive to temperature changes (especially cold) or pressure (by edema or mechanical force), resulting in the sensation of severe pain.







### 11.25 FACIAL NERVE BRANCHES AND THE PAROTID GLAND

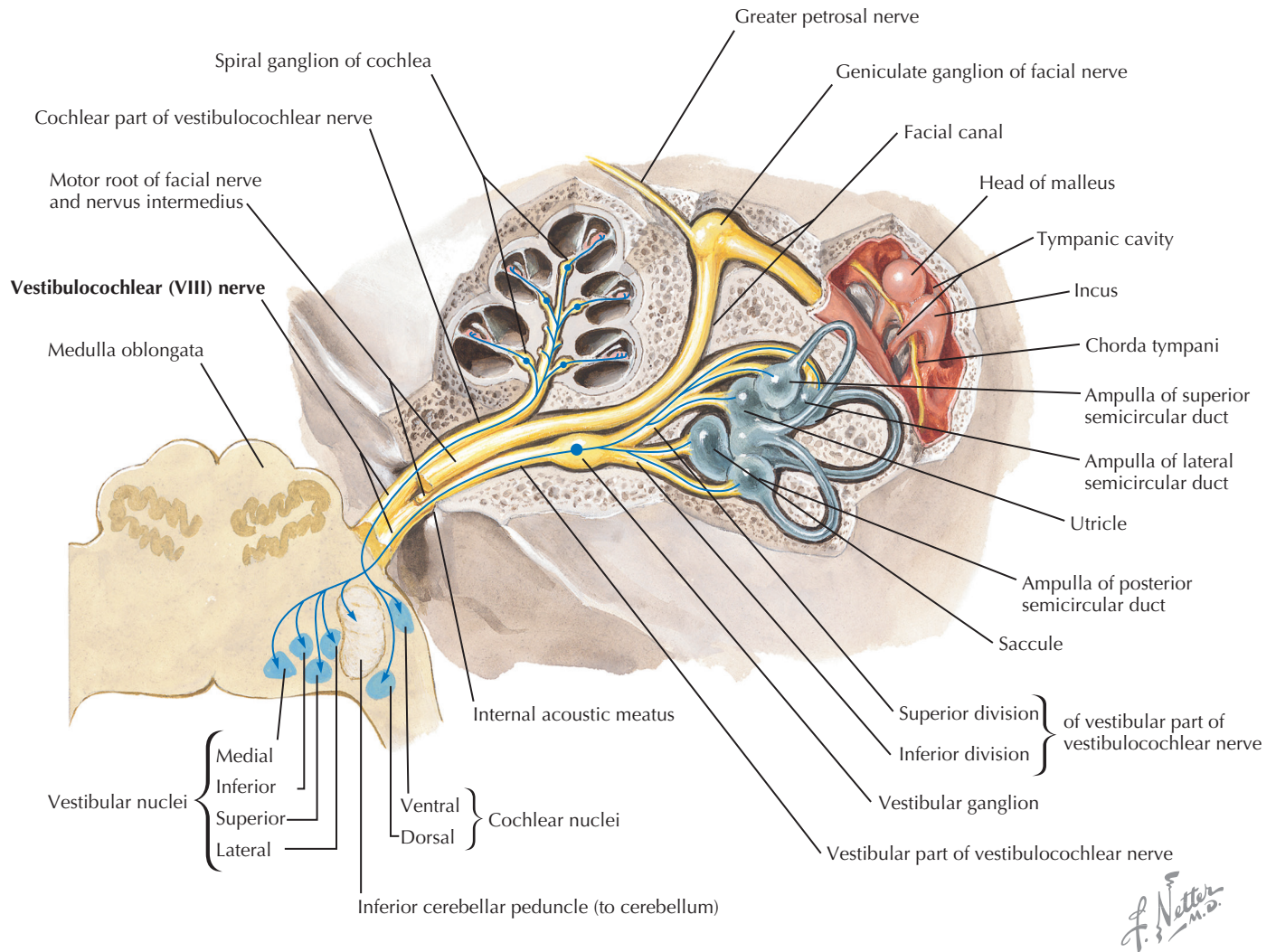
The facial nerve and its branches directly penetrate the parotid gland. Surgical procedures in this region of the face, particularly those performed to remove mass lesions, may damage the facial nerve, resulting in facial palsy in affected muscles.

#### CLINICAL POINT

Bell's palsy, the most common disorder of CN VII, usually occurs acutely, over the course of a few hours to a day or so, and results in weak or paralyzed muscles on one side of the face. Some patients report previous retroauricular pain, decreased tearing, or hyperacusis for a day or two. The facial palsy involves all of the muscles on the affected side, unlike a central facial palsy resulting from a lesion in the contralateral genu of the internal capsule, which affects only the lower part of the face. In Bell's palsy, the ipsilateral forehead does not wrinkle, the eye cannot be closed, the face appears smooth, and the

corner of the mouth droops. Viral infections (especially herpes simplex I) or inflammation may precipitate Bell's palsy; less commonly, Lyme disease, HIV, diabetes, sarcoidosis, or another infection may be the cause. Sensory loss is not part of the disorder, although loss of taste sensation on the anterior two thirds of the tongue, supplied by CN VII, may occur if the nerve is affected proximal to its merging with the chorda tympani. Involvement of the nerve to the stapedius muscle results in sensitivity to loud sounds (hyperacusis). Recovery can occur within a few weeks or months, particularly if only partial damage to the nerve has occurred and only some weakness has been present. With profound paralysis of facial muscles, the regenerative process may take as long as 2 years. During such a regenerative process, some regenerating nerve fibers may sprout to aberrant sites; former autonomic fibers that innervated salivary glands may be redirected to the lacrimal glands, resulting in "crocodile tears" or an abnormal gustatory-lacrimal reflex. Some aberrant regenerating facial nerve fibers may reach the wrong muscle fibers, resulting in tics, spasms, dyskinesias, or contractures.





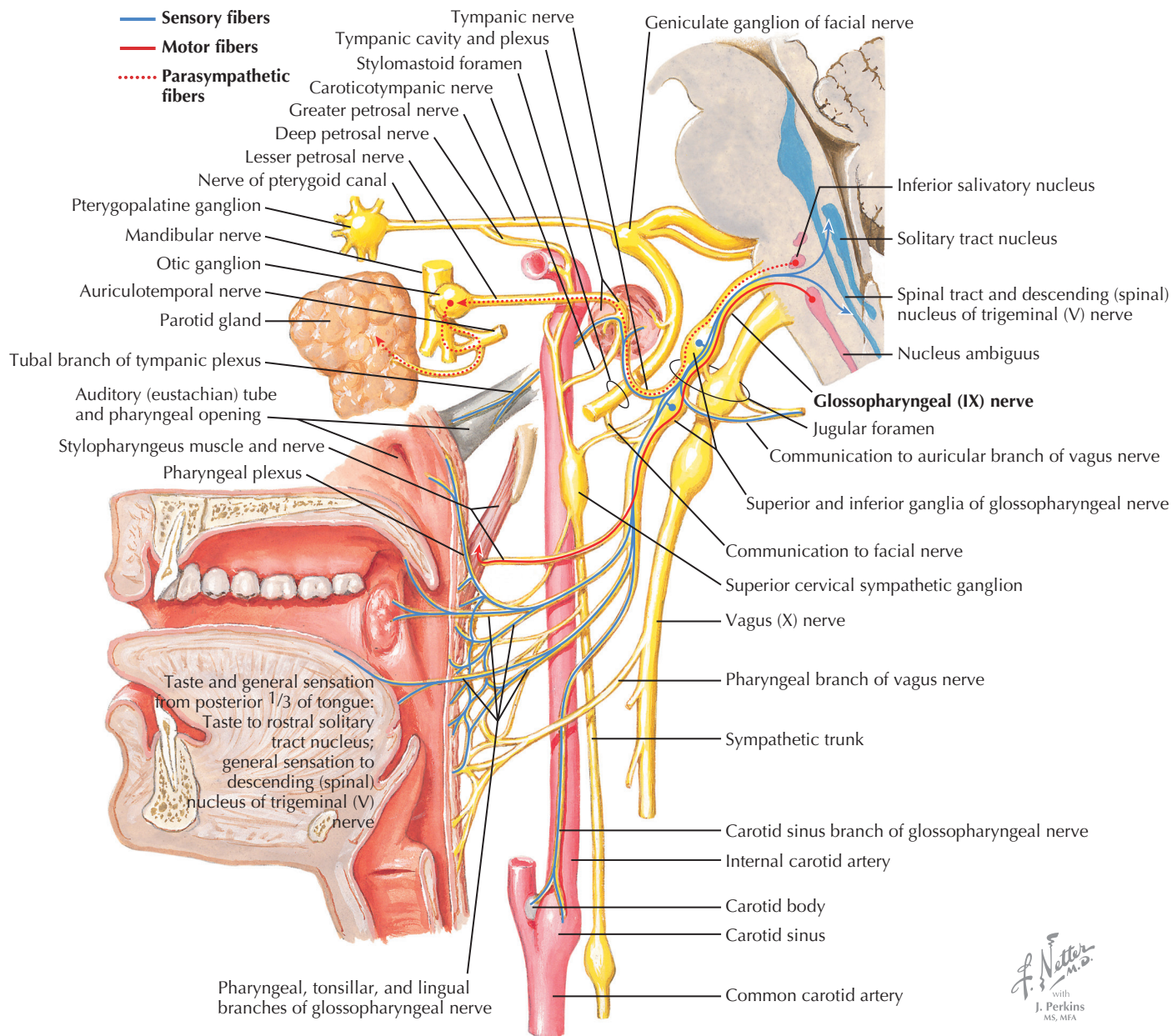
*F. Netter M.D.*

### 11.26 VESTIBULOCOCHLEAR NERVE (VIII)

The vestibulocochlear nerve (CN VIII) arises from bipolar primary sensory neurons in the vestibular ganglion (Scarpa's ganglion) and the spiral (cochlear) ganglion. The peripheral process of the vestibular ganglion neurons innervates hair cells in the utricle and saccule that respond to linear acceleration (gravity) and in the ampullae of the semicircular ducts that respond to angular acceleration (movement). The utricle, the saccule, and the semicircular ducts provide neural signals for coordination and equilibration of position and for movement of the head and neck. The central processes of the vestibular ganglion cells terminate in vestibular nuclei (medial, lateral, superior, and inferior) in the medulla and pons and in the cerebellum. The peripheral processes of spiral ganglion cells innervate hair cells that lie along the cochlear duct in the organ of Corti. They convey hearing information via central axonal processes into the cochlear nuclei (dorsal and ventral). A lesion in CN VIII results in ipsilateral deafness, vertigo, and loss of equilibrium.

#### CLINICAL POINT

The vestibulocochlear nerve emerges from the ventrolateral margin of the brain stem near the junction of the medulla, pons, and cerebellum (the cerebellopontine angle). At this site, Schwann cell tumors of CN VIII, acoustic schwannomas, can arise, usually from the vestibular portion of CN VIII. Initial irritation of the vestibular division of CN VIII can result in vertigo, dizziness, nausea, and unsteadiness or spatial disorientation. These symptoms persist with nerve destruction. Initial irritation of the auditory division of CN VIII by a schwannoma may first produce tinnitus, followed by slow loss of hearing and the inability to determine the direction from which a sound is coming. As nerve destruction occurs, tinnitus diminishes and ipsilateral deafness ensues. Because of the proximity of CNs VII and VIII, acoustic schwannomas also often produce ipsilateral facial paralysis or palsy. The tumor may extend rostrally to the trigeminal nerve or caudally to the glossopharyngeal and vagus nerves and also may affect the adjacent brain stem and cerebellum. At this point, hydrocephalus and increased intracranial pressure can occur.



### 11.27 GLOSSOPHARYNGEAL NERVE (IX)

CN IX is a mixed nerve with motor, parasympathetic, and sensory components. Motor fibers from the nucleus ambiguus supply the stylopharyngeus muscle and may assist in the innervation of pharyngeal muscles for swallowing. Preganglionic parasympathetic axons from the inferior salivatory nucleus travel with CN IX to the otic ganglion, whose neurons innervate the parotid and mucous glands. Special sensory axons from the petrosal (inferior) ganglion carry information from taste buds on the posterior one third of the tongue (including numerous taste buds in the vallate papillae) and part of the soft palate. These axons terminate in the rostral portion of nucleus solitarius. Axons from additional primary sensory neurons in the inferior ganglion also carry general sensation from the posterior one third of the tongue and from the pharynx, the fauces, the tonsils, the tympanic cavity, the eustachian tube, and the mastoid cells. The central axon branches terminate in the descending (spinal) nucleus of CN V. The general sensory fibers from the pharynx provide the afferent

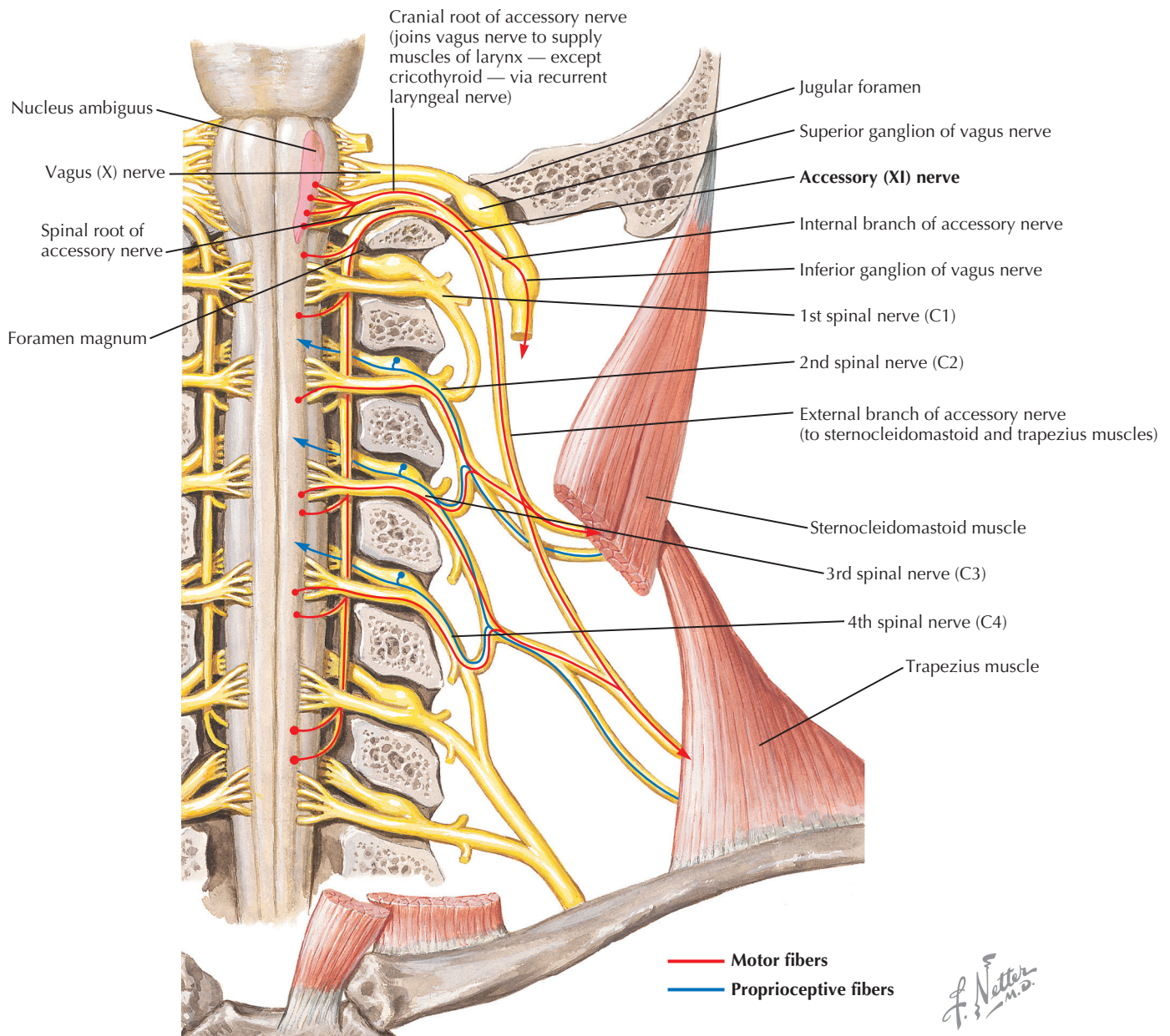
limb of the gag reflex. Additional primary sensory neurons innervate the carotid body (chemoreception of carbon dioxide) and the carotid sinus (baroreceptors) and convey their central axons to the caudal nucleus solitarius (*solitary tract nucleus*). Primary sensory neurons in the superior ganglion innervate a small region behind the ear and convey general sensation into the descending nucleus of CN V.

#### CLINICAL POINT

The glossopharyngeal nerve can be affected by brief, excruciating paroxysms of pain (glossopharyngeal neuralgia) similar to those experienced in trigeminal neuralgia. The pain originates in the throat (tonsillar fossa) or sometimes the jaw and radiates to the ear. Some patients experience pain in the tongue, face, or jaw. The triggering activity is usually swallowing, coughing, sneezing, or yawning. If the irritative process activates glossopharyngeal afferents associated with brain stem vasomotor responses, the patient may experience bradycardia and syncope. The treatment of glossopharyngeal neuralgia is similar to treatment of trigeminal neuralgia. Successful treatment also has occurred surgically through decompression of a tortuous aberrant vessel.

*J. Natter*  
M.D.  
with  
J. Perkins  
MS, MFA





### 11.28 ACCESSORY NERVE (XI)

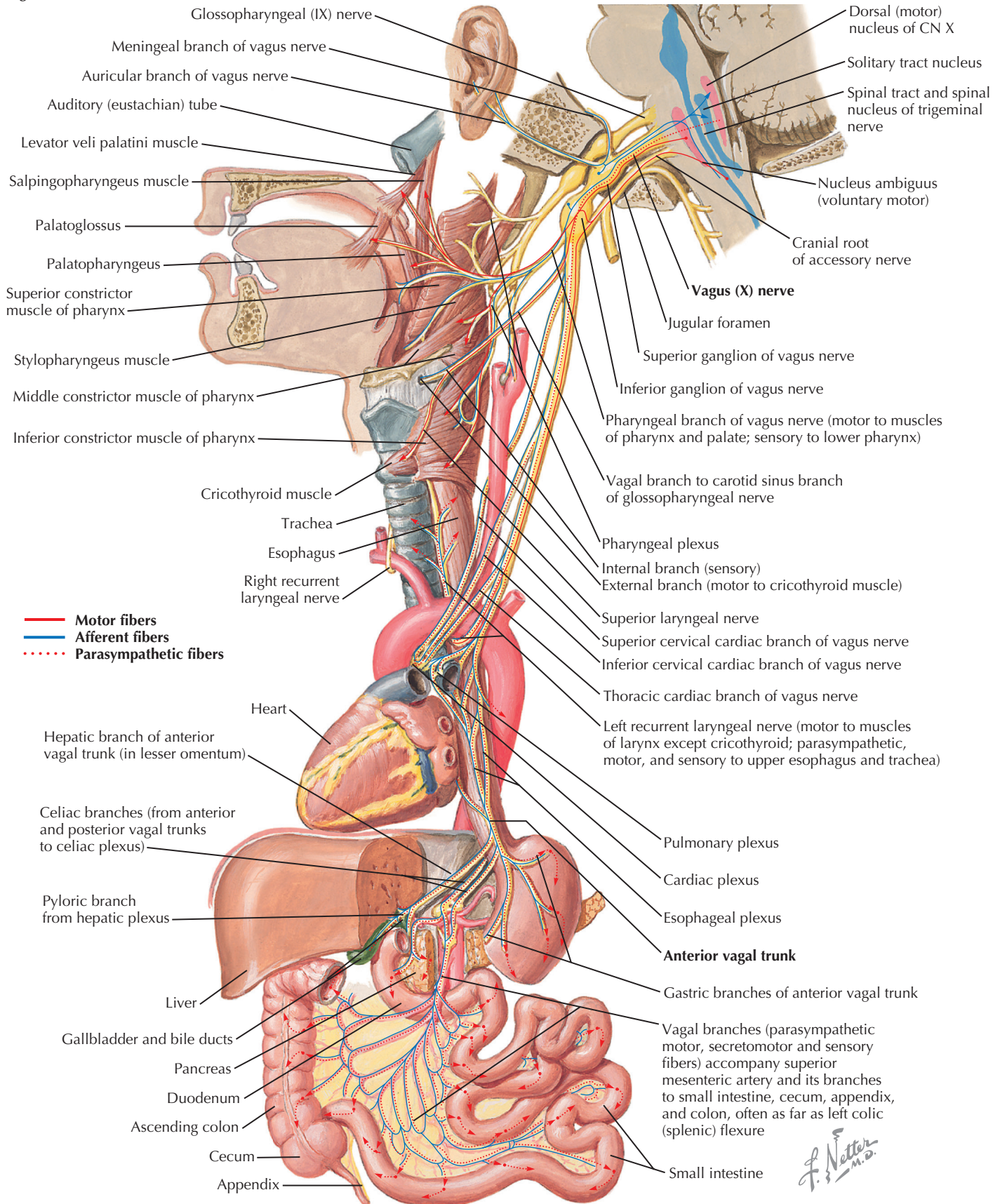
The accessory nerve (CN XI) is a motor nerve with cranial and spinal portions. The cranial portion arises from LMNs at the caudal end of the nucleus ambiguus; the axons travel through an internal branch that distributes with the pharyngeal and laryngeal branches of the vagus nerve (CN X) and with nerves to the soft palate. These axons often are considered to be part of CN X. The spinal portion arises from LMNs in the lateral part of the upper four or five segments of the cervical spinal cord. The axons then emerge as rootlets from the lateral margin of the spinal cord, ascend behind the denticulate ligaments, and coalesce as a single nerve. This nerve then ascends through the foramen magnum and joins the vagus nerve to exit through the jugular foramen. The LMNs of the spinal accessory nerve supply the sternocleidomastoid muscle and the upper two thirds of the trapezius muscle. Damage to this division of CN XI results in weakness in head rotation and shoulder elevation.

#### CLINICAL POINT

The cranial portion of the accessory nerve is derived from the nucleus ambiguus and has been considered to be part of the vagal complex. The spinal accessory nerve derives from LMNs of the upper segments (C1–C4) of the cervical spinal cord; it ascends through the foramen magnum and emerges with cranial nerves IX and X through the jugular foramen. Tumors, meningitis, and trauma may damage CN XI, although these lesions commonly damage nerves IX and X as well. LMN disorders, such as polio or amyotrophic lateral sclerosis or compression of the foramen magnum as in Arnold-Chiari malformation, can damage the spinal accessory nerve on one side. This results in ipsilateral flaccid paralysis of the sternocleidomastoid muscle and the upper two thirds of the trapezius, causing atrophy and loss of tone. The patient has great difficulty turning his or her head to the opposite side (sternocleidomastoid). The shoulder hangs downward, with caudal and lateral displacement of the scapula, and the arm cannot be raised more than 90 degrees. In circumstances in which bilateral damage occurs to the spinal accessory nucleus (as in amyotrophic lateral sclerosis), the bilateral denervation of the sternocleidomastoid leaves the patient unable to hold up his or her head.



# Vagus (X) Nerve



## Vagus Nerve (X)

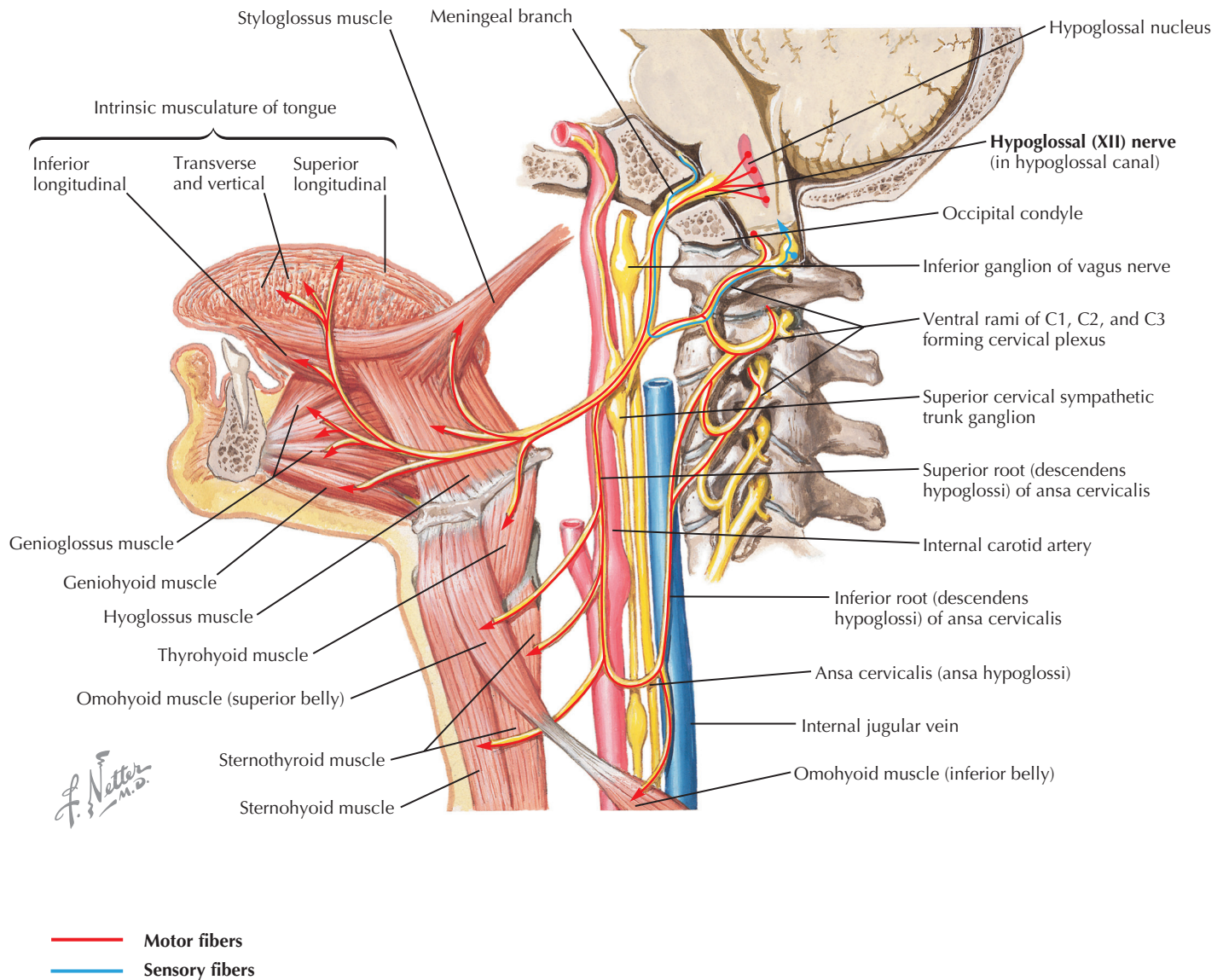
### 11.29 VAGUS NERVE (X)

The vagus nerve (CN X) is a mixed nerve with motor, parasympathetic, and sensory components. LMN axons from neurons in the nucleus ambiguus in the medulla supply muscles of the soft palate, the pharynx, and the larynx and control speaking and swallowing. A lesion in these axons results in hoarseness, dysphagia, and decreased gag reflex (efferent limb). Preganglionic parasympathetic axons from neurons in the dorsal motor (autonomic) nucleus of CN X in the medulla distribute to intramural ganglia associated with thoracic and abdominal viscera and supply autonomic innervation to the heart, the lungs, and the gastrointestinal tract to the descending colon. Special sensory axons from the nodose (inferior) ganglion, which carry information from taste buds in the posterior pharynx (found mainly in children), send central branches to terminate in the rostral nucleus solitarius. Primary sensory axons from the inferior ganglion also convey general sensation from the larynx, the pharynx, and the tho-

racic and abdominal viscera and terminate mainly in the caudal nucleus solitarius. Primary sensory axons from the superior (jugular) ganglion convey general sensation from the external auditory meatus and terminate in the descending (spinal) nucleus of CN V.

#### CLINICAL POINT

The vagus nerve emerges from the lateral surface of the medulla and can be involved in both intracranial and extracranial pathology. Intracranially, this nerve can be damaged by a tumor, hematoma, vascular infarct, aneurysm, meningitis, and other disorders. Extracranially, the vagus nerve can be damaged by a tumor, aneurysm, trauma, or infectious process. Unilateral damage to the vagus nerve results in (1) drooping of the soft palate, with the intact contralateral soft palate pulled to the opposite side during phonation, accompanied by nasal speech; (2) hoarseness resulting from involvement of the nucleus ambiguus fibers that extend to the laryngeal muscles; (3) ipsilateral laryngeal anesthesia; and (4) tachycardia and arrhythmias in some instances.



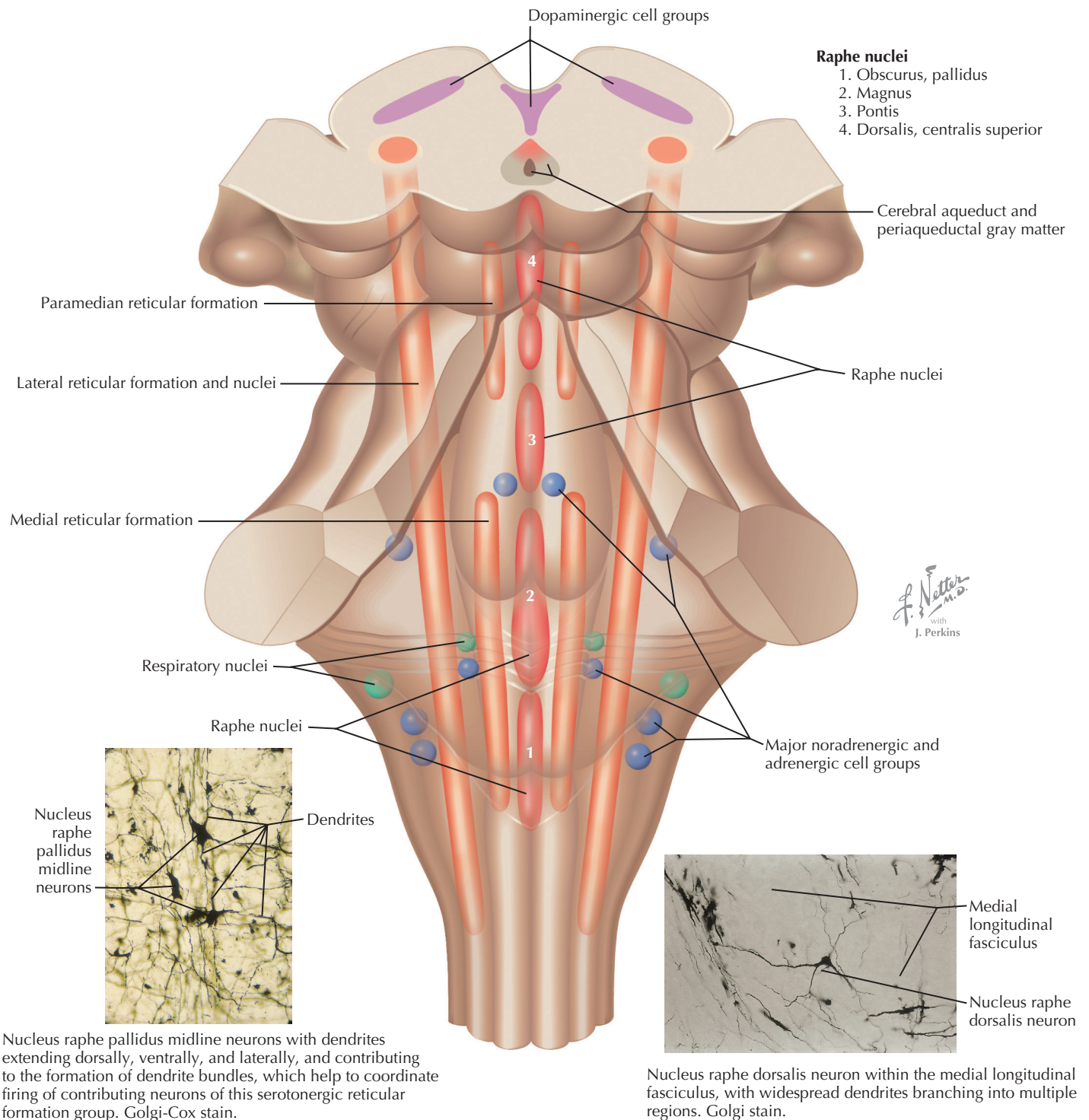
### 11.30 HYPOGLOSSAL NERVE (XII)

The hypoglossal nerve (CN XII) is a motor nerve. LMNs in the hypoglossal nucleus of the caudal medulla exit from the ventral surface of the medulla in the preolivary sulcus (between the medullary pyramid and the inferior olive) to innervate the extrinsic muscles of the tongue (the hyoglossus, styloglossus, chondroglossus, and genioglossus muscles) and the intrinsic muscles of the tongue (the superior and inferior longitudinal, transverse, and vertical lingual muscles). Damage to this nerve leads to weakness of the ipsilateral tongue muscles; the tongue, when protruded, deviates toward the weak side because of the unopposed action of the innervated contralateral genioglossus muscle.

#### CLINICAL POINT

The hypoglossal nerve emerges from the ventral surface of the medulla just lateral to the medullary pyramids. The emerging hypoglossal nerve fibers can be damaged intracranially by a paramedian infarct (that also damages the pyramid and medial lemniscus, producing a so-called alternating hemiplegia) or can be damaged peripherally by a meningeal tumor, a metastatic tumor, or bony overgrowth or as an unwanted consequence of a carotid endarterectomy. Hypoglossal nerve damage on one side produces flaccid paralysis of the ipsilateral tongue musculature, accompanied by atrophy. An attempt to protrude the tongue results in deviation of the tongue toward the weak side because of the unopposed actions of the intact genioglossus muscle. As damage to CN XII progresses, fasciculations can be seen on the ipsilateral tongue up to the point where total denervation occurs.



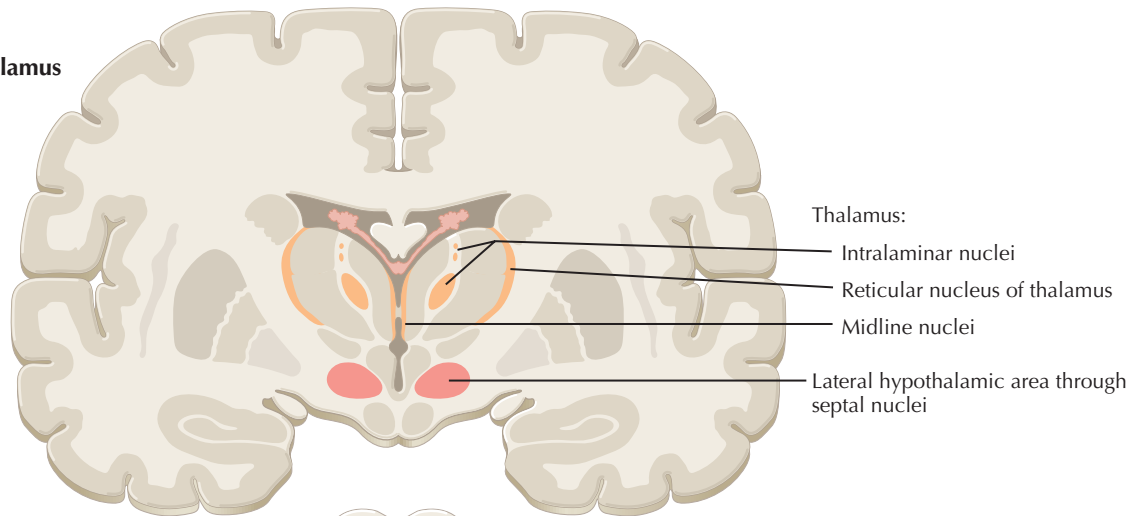
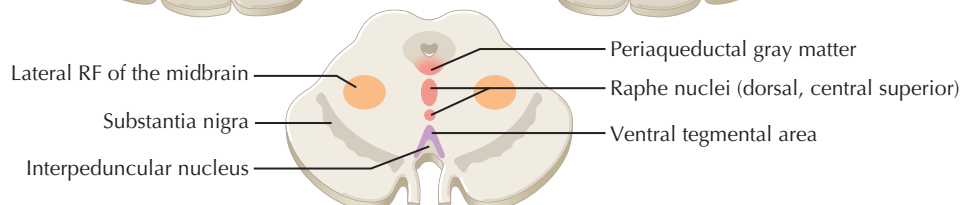
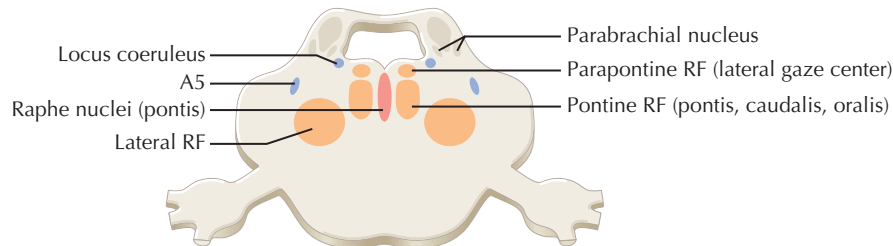
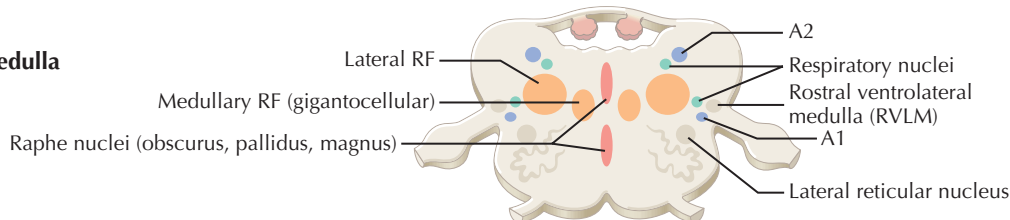
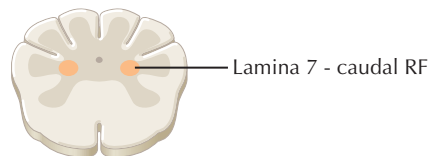


## RETICULAR FORMATION

### 11.31 RETICULAR FORMATION: GENERAL PATTERN OF NUCLEI IN THE BRAIN STEM

The reticular formation (RF), the neuronal core of the brain stem, consists of neurons with characteristic isodendritic morphology. The RF extends from the rostral spinal cord through the hypothalamus into the septal region. RF neurons are large cells with axonal arborizations that terminate at a distance from their cell bodies and dendritic tree; they are not interneurons. The major nuclei of the RF are found in a lateral

zone (predominantly sensory functions), a medial zone (predominantly motor functions), and a column of raphe nuclei (serotonergic neurons). The serotonergic neurons exert mainly modulatory influences on their targets. The catecholaminergic neurons (locus coeruleus, tegmental noradrenergic, and adrenergic groups) in several regions of the RF have widespread projections and exert mainly modulatory influences on their targets. The dopaminergic neurons of the midbrain are included in this illustration, although some experts question whether they are RF neurons.

**A. Thalamus and hypothalamus****B. Midbrain****C. Pons****D. Medulla****E. Spinal cord–medullary junction**

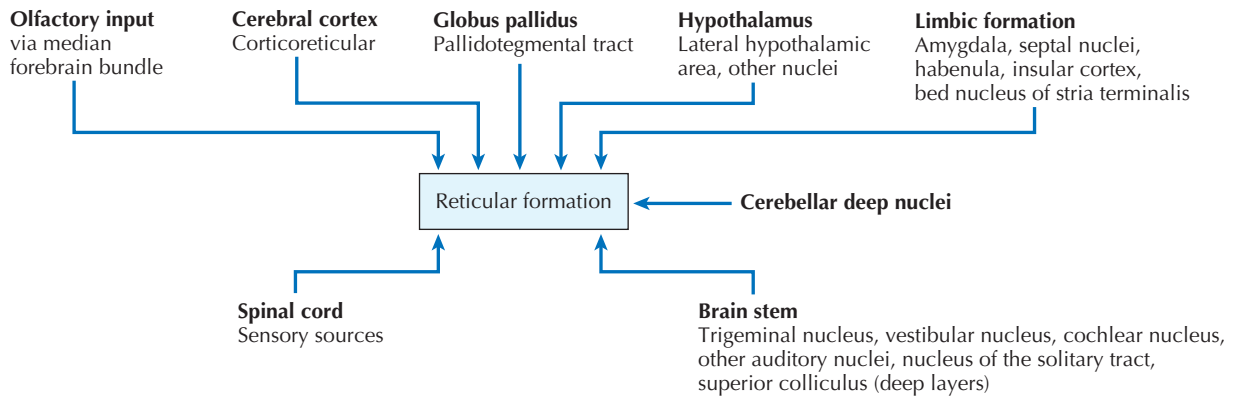
**J. Perkins**  
MS, MFA

### 11.32 RETICULAR FORMATION: NUCLEI AND AREAS IN THE BRAIN STEM AND DIENCEPHALON

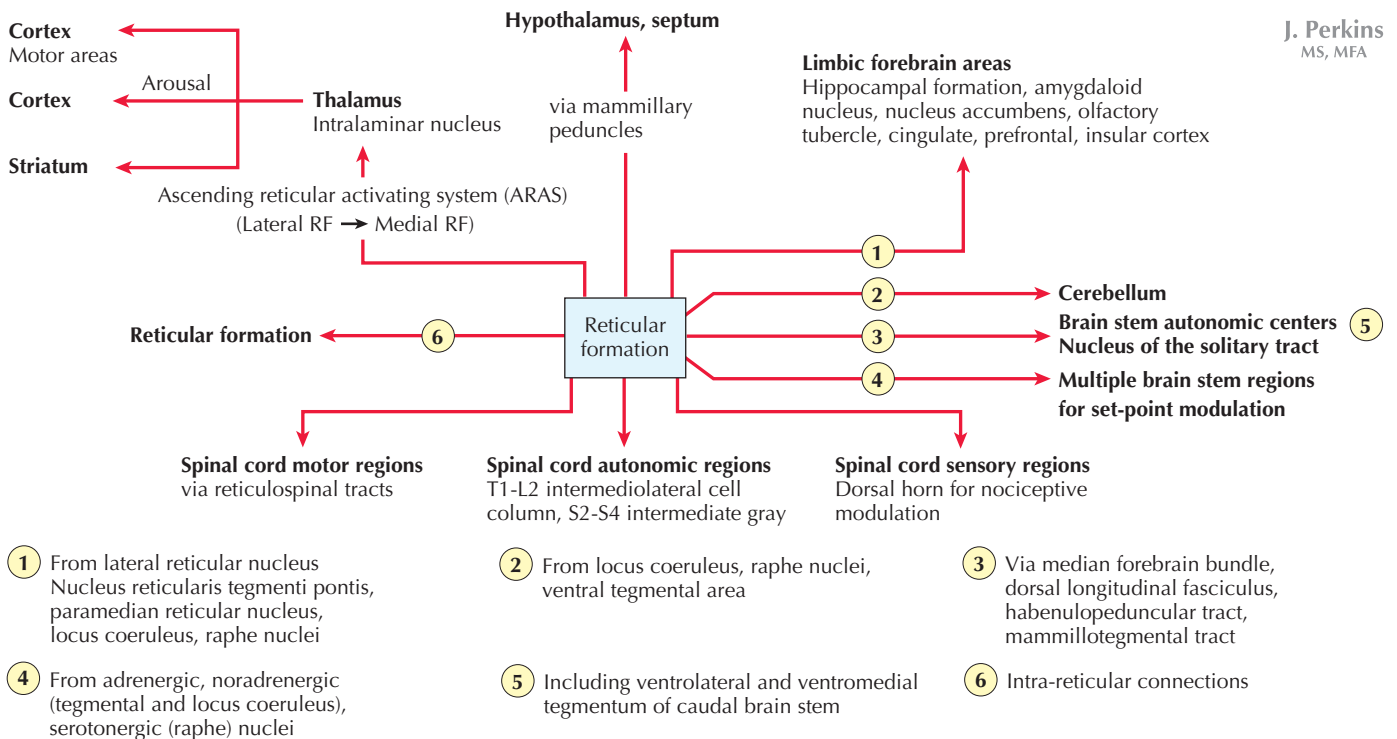
Many of the named nuclei of the RF are present in the medulla, the pons, and the midbrain. Important medial RF groups include the medullary (gigantocellular) and the pontine (caudal and rostral) RF regions, which are involved in reticulospinal regulation of spinal cord LMNs; and the parapontine RF, also known as the horizontal (lateral) gaze center. Lateral RF areas and nuclei (such as the lateral reticular nucleus) are involved in polymodal sensory functions. RF respiratory and

cardiovascular neurons are found in the medulla. Catecholaminergic neurons are found in the locus coeruleus (group A6), and tegmental groups denoted here as groups A1, A2, and A5 (norepinephrine-containing neurons). Raphe nuclei are found in the midline and in wings of cells that extend laterally. The core of the RF continues rostrally from the lateral regions of the brain stem into the lateral hypothalamic area and extends through the hypothalamus to the septal nuclei. Several thalamic nuclei (intralaminar, midline, and reticular nucleus of the thalamus) also are classified as part of the RF.

## A. Major afferent connections to the reticular formation



## B. Major efferent connections from the reticular formation

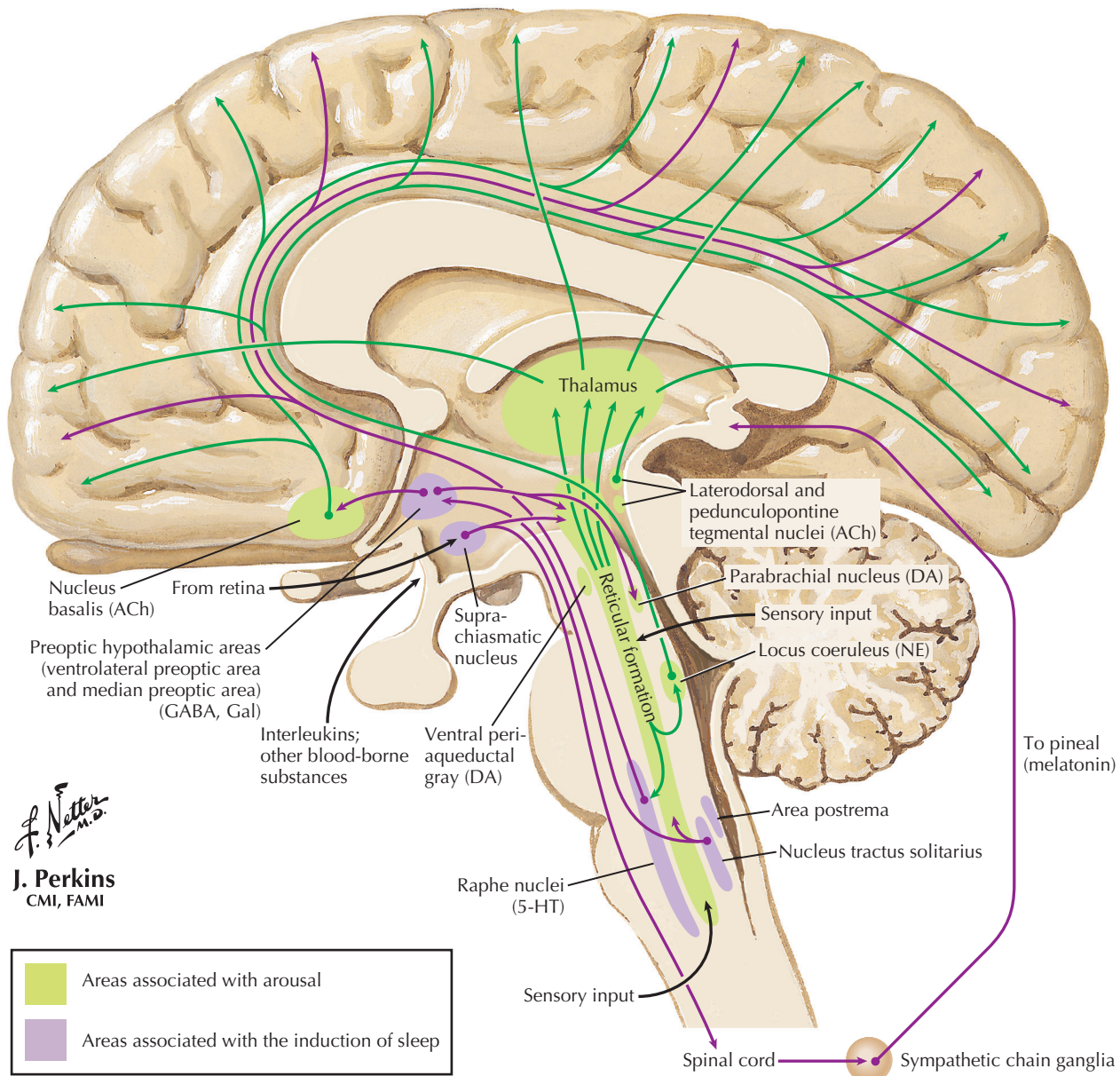
J. Perkins  
MS, MFA

## 11.33 MAJOR AFFERENT AND EFFERENT CONNECTIONS TO THE RETICULAR FORMATION

**A**, Extensive sensory information from spinal cord somato-sensory sources (particularly nociceptive information) and from virtually all brain stem sensory modalities is sent to the lateral regions of the RF. Olfactory input arrives through olfactory tract projections into forebrain regions. Many limbic and hypothalamic structures provide input into the RF, particularly for visceral and autonomic regulatory functions. The cerebral cortex, the globus pallidus, and the cerebellum also provide input into the RF medial zones involved in motor regulation. **B**, The ascending reticular activating system (ARAS) of the RF is responsible for consciousness and arousal.

It projects through nonspecific nuclei of the thalamus to the cerebral cortex; lesions in this area lead to coma. The RF sends extensive axonal projections to sensory, motor, and autonomic regions of the spinal cord, modulating nociceptive input, pre-ganglionic autonomic outflow, and LMN outflow, respectively. The RF sends extensive connections to brain stem nuclei (such as nucleus tractus solitarius) and to autonomic regulatory centers and nuclei for modulation of visceral functions. Efferent RF projections to the hypothalamus, septal nuclei, and limbic forebrain areas help to modulate visceral autonomic functions, neuroendocrine outflow, and emotional responsiveness and behavior. Efferent RF projections to the cerebellum and basal ganglia participate in modulating UMN control of LMNs.



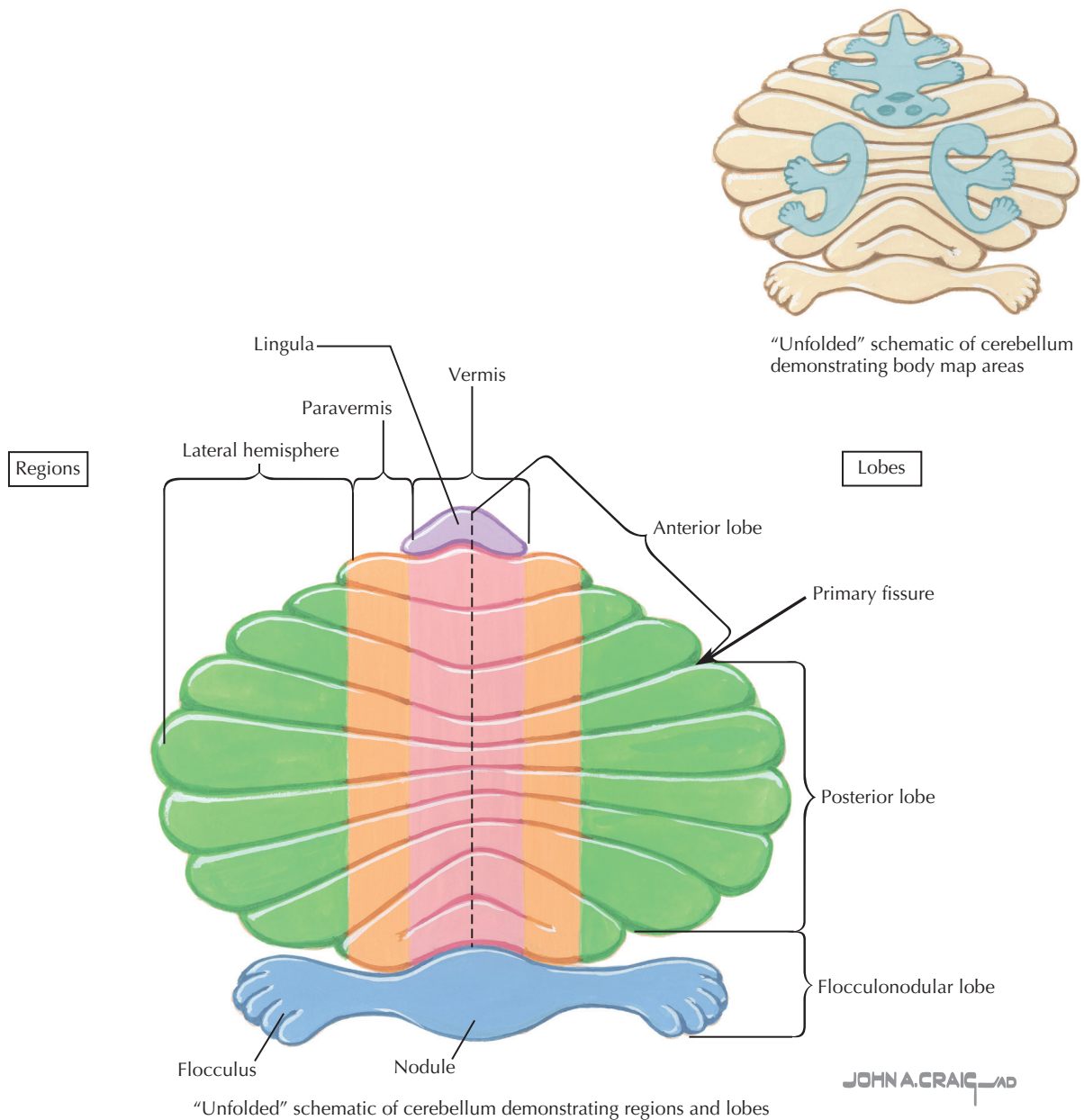


*J. Netter M.D.*  
**J. Perkins**  
 CMI, FAMI

### 11.34 SLEEP-WAKEFULNESS CONTROL

Sleep is a normal physiological state involving a cyclic temporary loss of consciousness; it is readily reversed by appropriate sensory stimuli. Sleep is an active process initiated by brain activity in several chemical-specific collections of neurons of the brain: (1) the locus coeruleus of the pons (noradrenergic); (2) the raphe nuclei of the medulla and pons (serotonergic); (3) the nucleus solitarius of the medulla; (4) the cholinergic neurons of the brain stem tegmentum (laterodorsal and pedunculo-pontine tegmental nuclei); (5) ventral periaqueductal gray (dopaminergic); (6) parabrachial nuclei; (7) the lateral RF, particularly in the pons; (8) several regions of the hypothalamus (anterior region, posterior region, preoptic area); (9) nuclei of the preoptic area (median preoptic nucleus, MnPO; and ventrolateral preoptic nucleus, VLPO); (10) the reticular nucleus of the thalamus; and (11) nucleus basalis (cholinergic). An ascending arousal system emanates from the rostral pons and caudal midbrain (monoamines, ACh, and glutamate neurons) and acts through thalamic relay nuclei and the thalamic reticular nucleus. Monoamine neurons from the upper brain stem also project directly to the cerebral cortex, along with cholinergic and histaminergic neurons, and

excite cortical circuits, enhancing their processing capabilities. These circuits are maximally active during wakefulness and slow their activity during non-REM sleep. Sleep is regulated by two neuronal groups in the preoptic area, the median preoptic nucleus (MnPO) and the ventrolateral preoptic nucleus (VLPO). Both of these regions innervate the entire ascending arousal system, using the inhibitory neurotransmitters GABA and galanin. The VLPO is active during sleep and can suppress the ascending arousal system. Circulating substances such as interleukin-1 beta can act on key sites in the hypothalamus and brain stem to influence components of sleep. Illness behavior involves enhanced slow-wave sleep induced by interleukin-1 beta and other inflammatory mediators. Sleep that does not involve rapid eye movement (REM), or slow-wave sleep, is initiated by hypothalamic neurons and other regions and is accompanied by decreased activity in the locus coeruleus and the cholinergic tegmental neurons. During REM sleep, activity in noradrenergic locus coeruleus neurons and serotonergic raphe neurons greatly diminishes, which prevents the cerebral cortex from attending to external stimuli. Dreams probably occur because the cortex is attending to internal stimuli provided by stored memories.



## CEREBELLUM

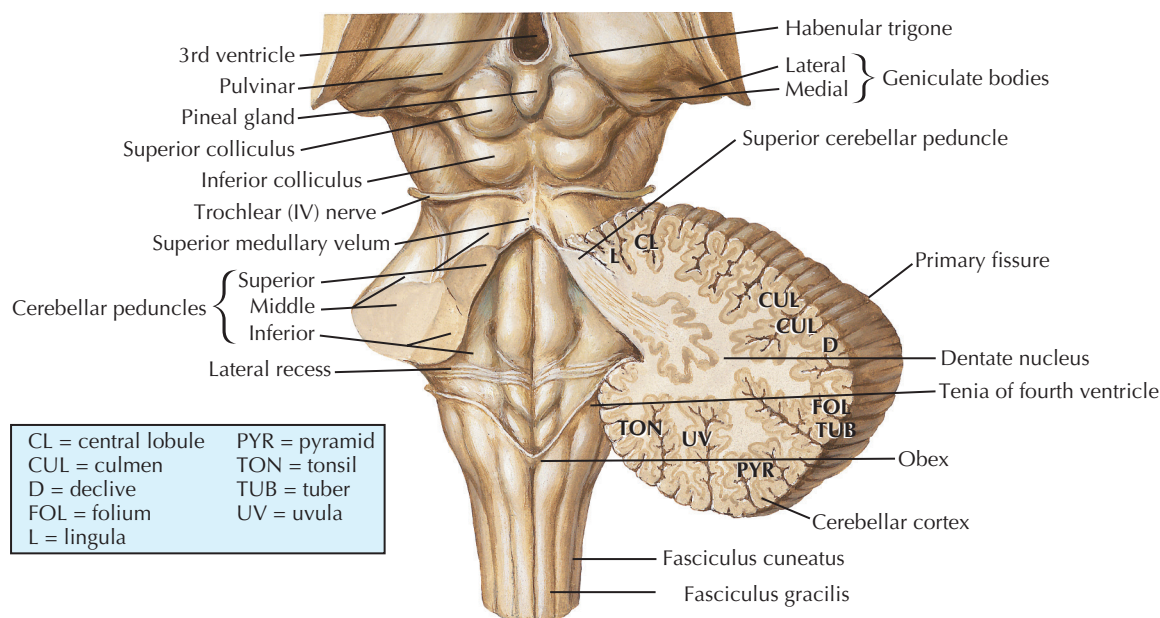
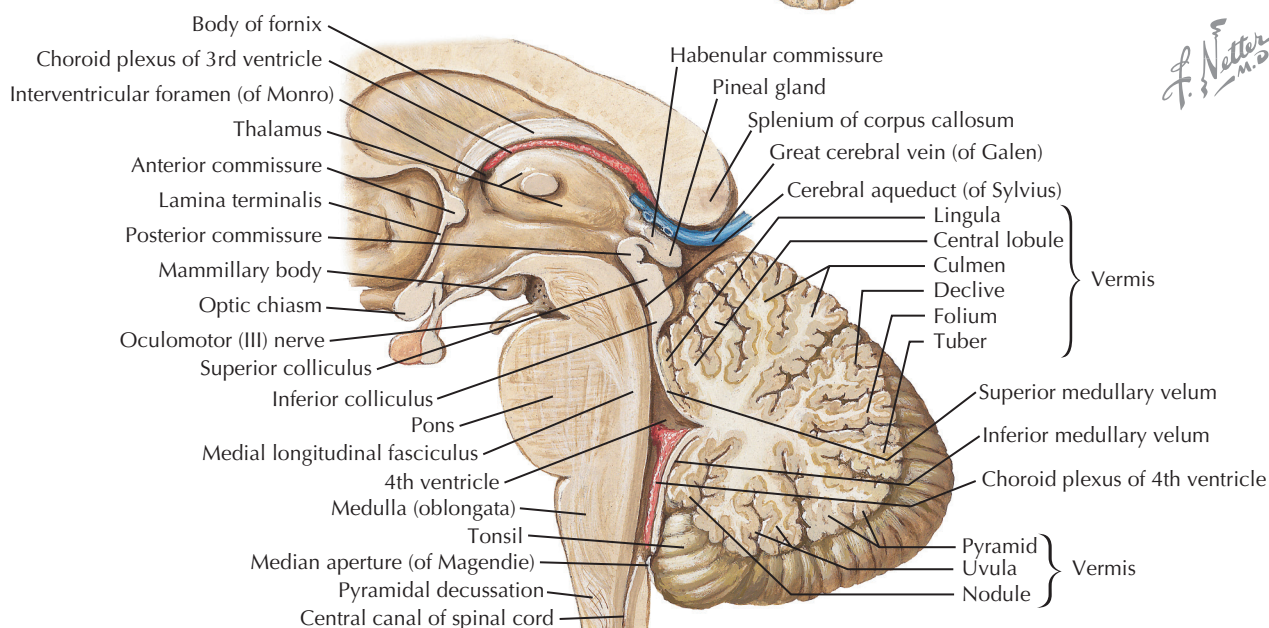
### 11.35 CEREBELLAR ORGANIZATION: LOBES AND REGIONS

The cerebellum is organized anatomically into three major lobes: (1) anterior, (2) posterior, and (3) flocculonodular. Distinct syndromes are associated with damage to each lobe. The functional organization of the cerebellar hemisphere follows a vertical organization: (1) vermis (midline); (2) paravermis; and (3) lateral hemispheres. Each of these functional regions is associated with specific deep nuclei (fastigial, globose and emboliform, and dentate, respectively) that help to regulate the activity of reticulospinal and vestibulospinal tracts, the rubrospinal tract, and the corticospinal tract, respectively. At least three representations of the body are mapped onto the cerebellar cortex. The cerebellar cortex has multiple, orderly, small infoldings, or convolutions, called folia.

#### CLINICAL POINT

The cerebellum demonstrates both a lobular organization (anterior lobe, posterior lobe, and flocculonodular lobe), commonly associated with cerebellar syndromes; and a longitudinal organization (vermis, paravermis, lateral hemispheres), commonly associated with regulatory control over specific groups of UMNs. The vascular supply to the cerebellum comes mainly from the superior, anterior inferior, and posterior inferior cerebellar arteries. The cerebellum is quite prone to intracerebellar bleeds and hematomas. The superior cerebellar artery has fine branches that can rupture in hypertensive conditions and damage the rostral cerebellum and deep nuclei such as the dentate nucleus. A cerebellar hematoma acts as a space-occupying lesion and also may induce further edema. As a result, increased intracranial pressure can occur, and the flow of cerebrospinal fluid can be disrupted, secondarily bringing about supratentorial increased intracranial pressure. The patient experiences headache, nausea and vomiting, and vertigo and then may lapse into a coma. Decerebrate posturing, blood pressure dysregulation, and respiratory failure may ensue. Without rapid drainage, such a hematoma is commonly fatal. Smaller intracerebellar bleeds result in ipsilateral symptoms that are characteristic of the affected region of cerebellum.



**A. Posterior view****B. Lateral view****11.36 CEREBELLAR ANATOMY: LOBULES**

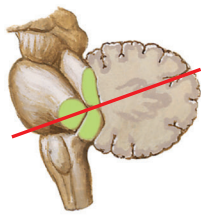
**A, Posterior view.** In this horizontal (axial) section through the right cerebellar hemisphere, the left hemisphere has been removed, the cerebellar peduncles cut, and the fourth ventricle opened to show the dorsal surface of the brain stem below. The cerebellar cortex is organized into 10 lobules. The cerebellar peduncles provide the large white matter regions through which afferents and efferents pass, connecting the cerebellum with the brain stem and diencephalon. **B, Lateral view.** The lobules of the cerebellum are shown in midsagittal section. Inputs into the cerebellar hemispheres show a similar general organization, with variation from lobule to lobule, particularly for noradrenergic inputs from the locus coeruleus. Inputs from a vast majority of nuclei projecting to the cerebellar hemispheres arrive as mossy fibers; the inferior olivary nucleus sends climbing fibers to end on Purkinje cell dendrites in the cerebellar hemispheres, and the locus coeruleus sends diffuse varicose inputs into all three layers of many regions of the cerebellar cortex. The deep nuclei provide the “coarse adjustment” upon which is superimposed the “fine adjustment” by

the cerebellar cortex. The cerebellar cortex sends its output via Purkinje cell projections, using gamma-aminobutyric acid (GABA) as the principal neurotransmitter, to deep nuclei, which in turn project to UMNs.

**CLINICAL POINT**

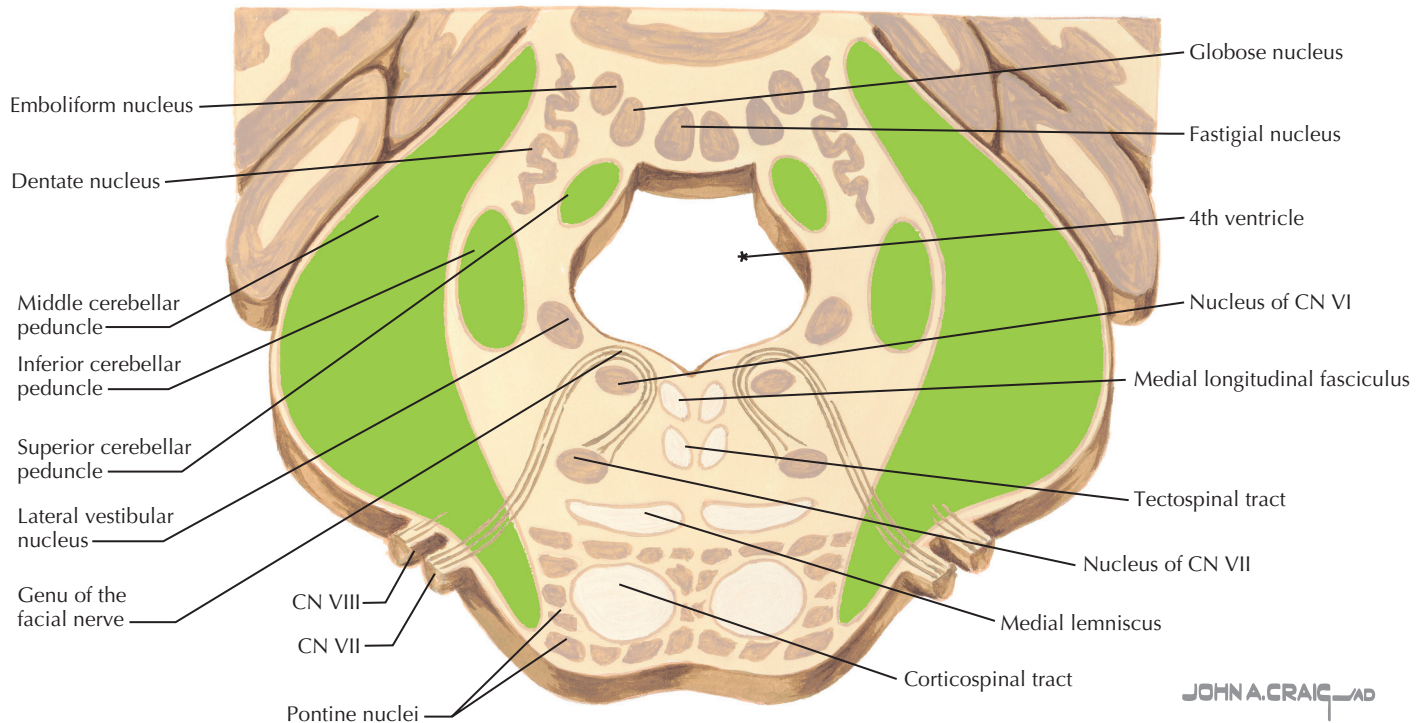
Cerebellar tumors commonly start in a specific region of the cerebellum. Cerebellar medulloblastomas are childhood malignant tumors that often begin in the flocculonodular lobe and are detected initially because of truncal ataxia and a broad-based uncoordinated gait. However, as the tumor slowly grows, it involves additional areas of the cerebellum by means of pressure or by invading neighboring areas. Then, in addition to the truncal ataxia, additional limb ataxia, dysmetria, dysidiadochokinesia, intention tremor, hypotonia, and other characteristics of lateral cerebellar damage are seen. Because the posterior fossa is involved, and not supratentorial regions, papilledema does not occur and does not provide a clue for diagnosis; rather, the increased posterior fossa pressure results in occipital headaches with nausea, vomiting, and nystagmus. The two most common cerebellar tumors of childhood are medulloblastomas, which can spread to adjacent portions of the CNS; and astrocytomas, which commonly are not highly invasive in the cerebellum but do grow as space-occupying masses.





Level of section

Peduncle	Input (efferents)	Output (efferents)
Inferior (restiform body)	Spinocerebellar Dorsal Rostral Cuneocerebellar Olive-cerebellar Reticulocerebellar Trigemino-cerebellar Raphe-cerebellar	Fastigiobulbar, Uncinate fasciculus } To vestibular and reticular nuclei  Direct cerebellovestibular (to lateral vestibular nucleus [LVN])
Juxtarestiform body	Vestibulospinal (primary, secondary)	
Middle (brachium pontis)	Pontocerebellar	
Superior (brachium conjunctivum)	Ventral spinocerebellar Trigemino-cerebellar Tectocerebellar Superior colliculus Inferior colliculus Coeruleo-cerebellar	Dentatothalamic Dentatorubral Dentoreticular Interpositus-rubral connections (globose, emboliform)



JOHN A. CRAIG MD

### 11.37 CEREBELLAR ANATOMY: DEEP NUCLEI AND CEREBELLAR PEDUNCLES

The deep cerebellar nuclei are found at the roof of the fourth ventricle in a cross-sectional view of the pons at the level of cranial motor nuclei for CNs VI and VII. The fastigial nucleus receives input from the vermis and sends projections to reticular and vestibular nuclei, the cells of origin of the reticulospinal and vestibulospinal tracts. Some vermal and flocculonodular Purkinje cells project directly to the lateral vestibular nuclei, which some authors consider to be a fifth deep cerebellar nucleus; this nucleus also is the UMN cell group for the vestibulospinal tract. The globose and emboliform nuclei receive input from the paravermis and project to the red nucleus, the cells of origin for the rubrospinal tract. The dentate nucleus receives input from the lateral hemispheres and projects to the ventrolateral and ventral anterior nuclei of the thalamus; these thalamic nuclei project to the cells of origin of the corticospinal and corticobulbar tracts. All three cerebellar peduncles can be seen in this cross-section. The table lists the major afferent and efferent projections through the three cerebellar peduncles and are depicted in color.

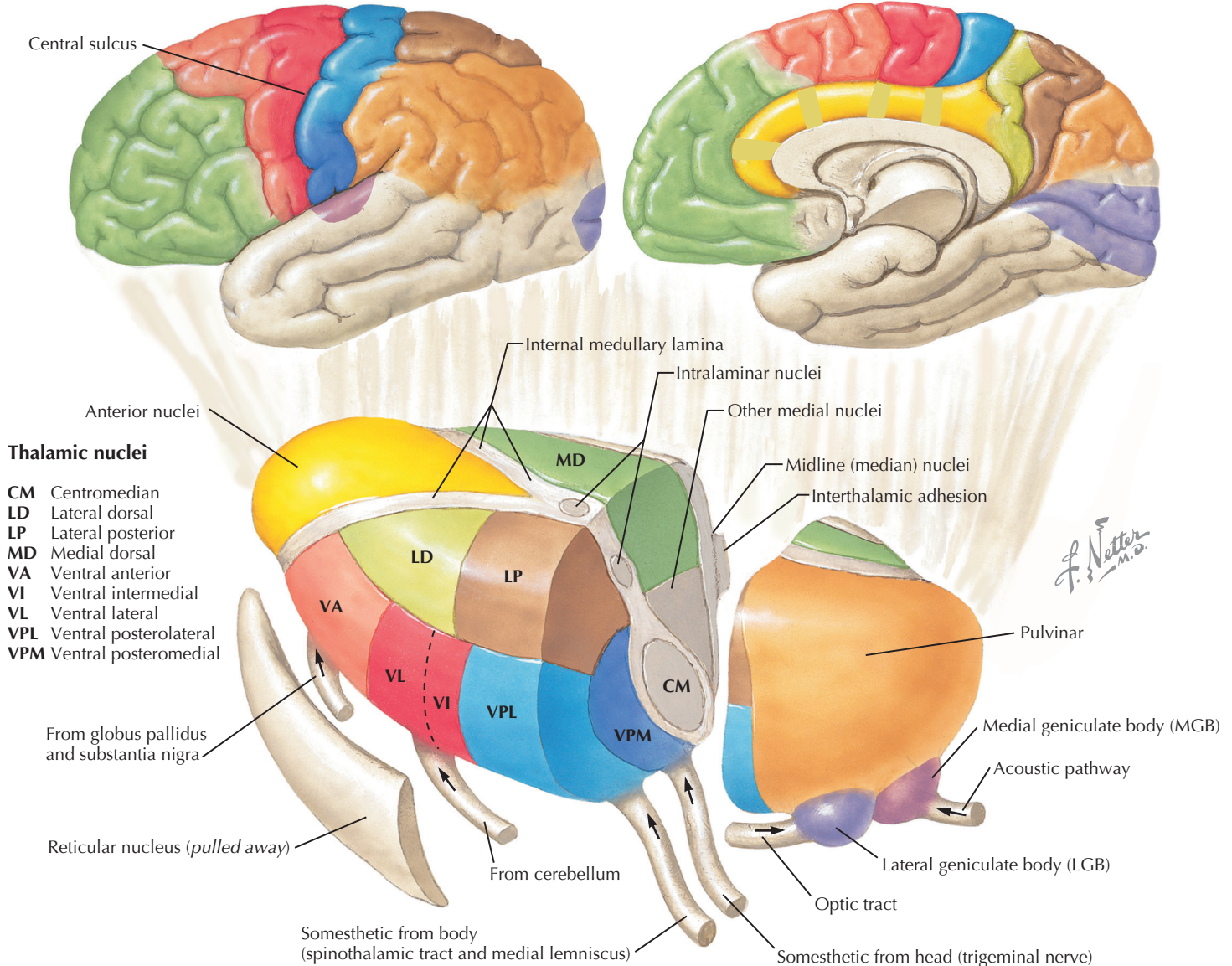
#### CLINICAL POINT

The inferior cerebellar peduncle conveys many afferents to the cerebellum from the spinocerebellar system, reticular formation, vestibular system, and trigeminal system, and it conveys efferents from the fastigial nucleus and flocculonodular lobe to vestibulospinal and reticulospinal UMN systems. The middle cerebellar peduncle mainly conveys afferents to the cerebellum from the cortico-ponto-cerebellar system. The superior cerebellar peduncle conveys selective afferents to the cerebellum and carries extensive efferents from the globose, emboliform, and dentate nuclei to the red nucleus and ventrolateral thalamus for regulation of the rubrospinal and corticospinal UMN systems. An infarct in the superior cerebellar artery can damage the blood supply to the superior and middle peduncles and the deep nuclei on one side. Lesions in these structures commonly have longer lasting and more severe clinical effects than lesions that affect only the cerebellar cortex. A superior cerebellar artery infarct can result in ipsilateral limb ataxia, dysmetria, dysidiadochokinesia, intention tremor, hypotonus, and other characteristics of lateral cerebellar damage. In addition, some midbrain structures are supplied by this artery; an infarct causes added brain stem problems, such as nystagmus and eye movement problems.

# 12

## DIENCEPHALON

- 12.1 [Thalamic Anatomy and Interconnections with the Cerebral Cortex](#)
- 12.2 [Hypothalamus and Pituitary Gland](#)
- 12.3 [Hypothalamic Nuclei](#)

**Thalamocortical radiations****12.1 THALAMIC ANATOMY AND INTERCONNECTIONS WITH THE CEREBRAL CORTEX**

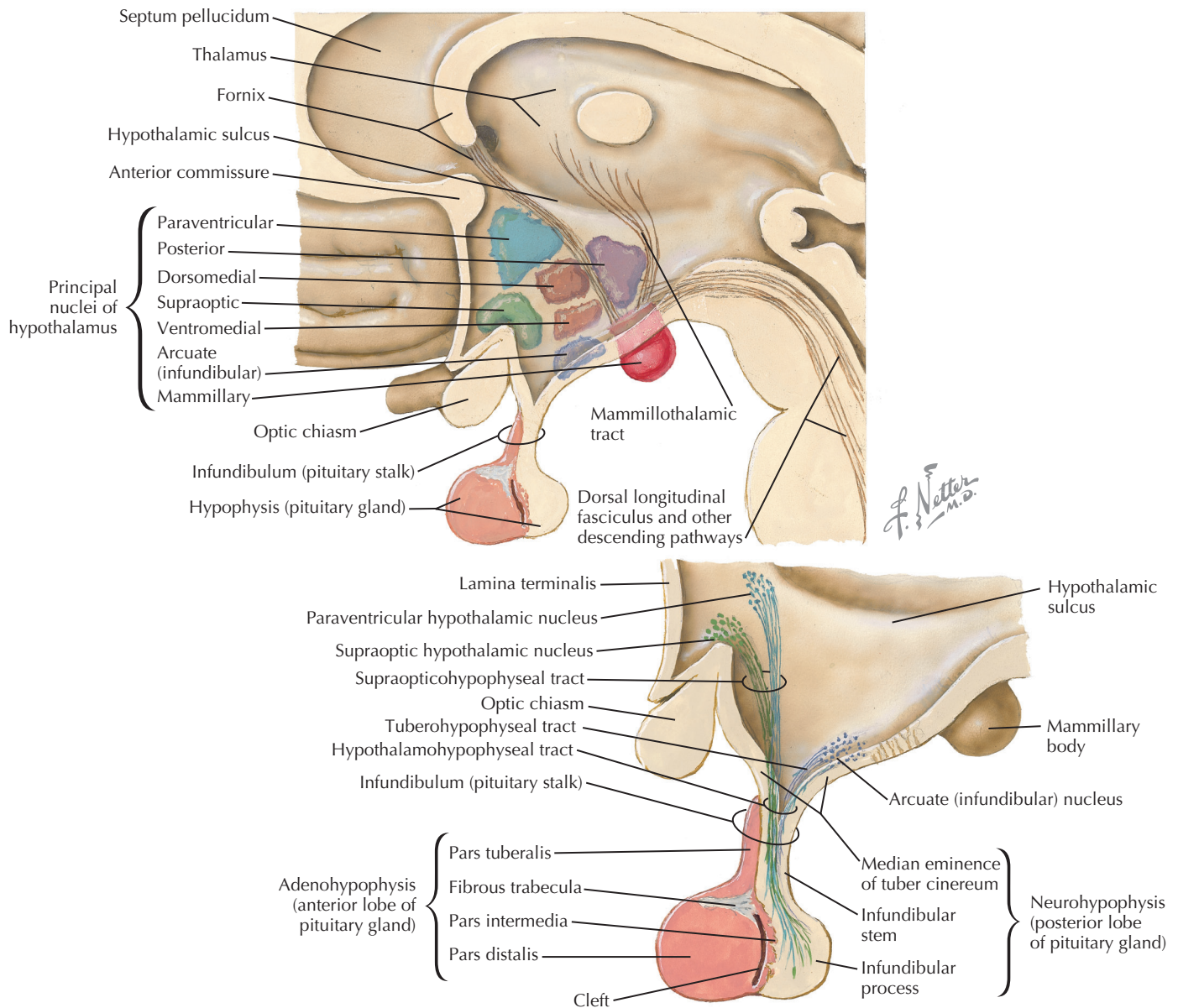
The thalamus, the gateway to the cerebral cortex, conveys extensive sensory, motor, and autonomic information from the brain stem and spinal cord to the cortex. All sensory projections to the cortex except olfaction are processed through thalamic nuclei. Thalamic nuclei are reciprocally interconnected with regions of cortex. Specific thalamic nuclei project to circumscribed regions of cortex. These nuclei include (1) sensory projection nuclei (VPL: somatosensory; VPM: trigeminal; LGB: visual; MGB: auditory; pulvinar: sensory); (2) motor-related nuclei (VL and VI: cerebellum; VA and VL: basal ganglia); (3) autonomic- and limbic-related nuclei (anterior and LD: cingulate cortex; MD: frontal and cingulate cortex); and (4) nuclei related to association areas (pulvinar and LP: parietal cortex). Nonspecific thalamic nuclei (intralaminar nuclei, such as CM, parafascicular, and medial VA) send diffuse connections to widespread regions of cerebral cortex and to other thalamic nuclei. The reticular nucleus of the thalamus helps to regulate the excitability of thalamic projec-

tion nuclei. Specific lesions of the thalamus can result in diminished sensory, motor, or autonomic activity related to loss of the specific modalities processed. Some thalamic lesions can lead to excruciating paroxysms of neuropathic pain, which is referred to as thalamic syndrome.

**CLINICAL POINT**

The thalamus has a complex blood supply that is derived extensively from the penetrating posterior cerebral, posterior communicating, and other nearby arteries. Thalamic nuclei are seldom individually affected by infarcts and lesions but are damaged along with nearby regions. Lesions that affect one side of the thalamus seldom produce permanent deficits unless sensory nuclei are involved. Thalamic lesions can result in changes in consciousness and alertness (intralaminar, reticular nuclei); affective behavior (medial dorsal, ventral anterior, intralaminar nuclei); memory functions (midline, medial, mammillary, and possibly anterior nuclei); motor activity (ventrolateral, ventral anterior, posterior, other nuclei); somatic sensation (ventral posterolateral and posteromedial nuclei); vision (lateral geniculate nuclei); and perceptions and hallucinations (dorsomedial, intralaminar nuclei). Medial dorsal lesions may produce a reciprocal disconnect with the prefrontal cortex and bring about a deficit in frontal functions.

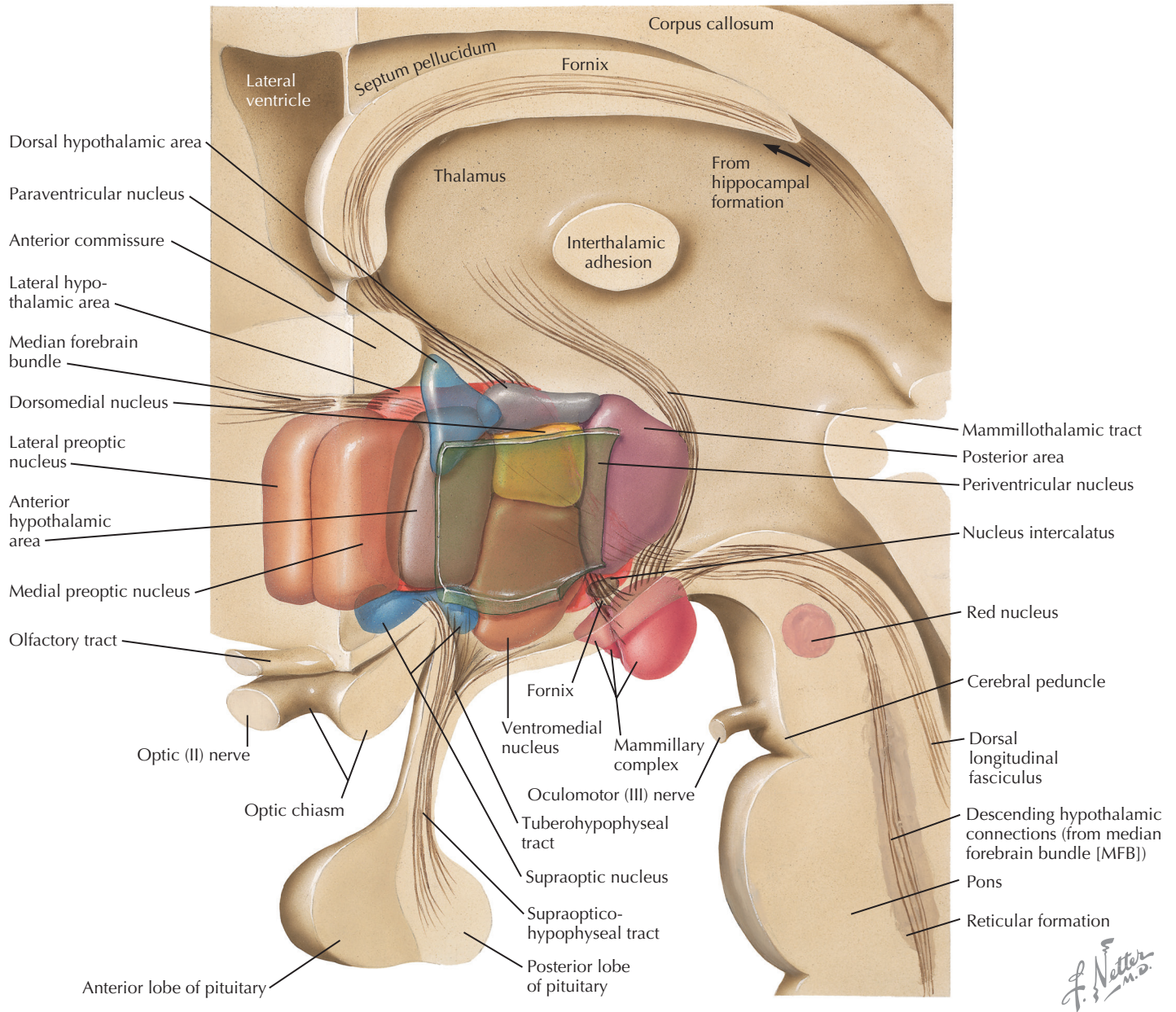




## 12.2 HYPOTHALAMUS AND PITUITARY GLAND

The hypothalamus is the major region of the central nervous system involved in neuroendocrine regulation and control of visceral functions, such as temperature regulation, food and appetite regulation, thirst and water balance, reproduction and sexual behavior, parturition and control of lactation, respiratory and cardiovascular regulation, gastrointestinal regulation, stress responses, and reparative states. The hypothalamus is located between the rostral midbrain and the lamina terminalis, ventral to the thalamus; it surrounds the third ventricle. The hypothalamus is subdivided in rostral-to-caudal zones (preoptic, anterior or supraoptic, tuberal, and mammillary or posterior) as well as medial-to-lateral zones (periventricular, medial, lateral). These zones contain some discrete nuclei and even discrete chemical-specific subnuclei,

such as the paraventricular nucleus (PVN) and more diffuse centers, regions, or areas (such as anterior, posterior, and lateral regions). The neuroendocrine portion of the hypothalamus consists of (1) magnocellular portions of the PVN and the supraoptic nucleus, which send axons directly to the posterior pituitary and release vasopressin and oxytocin into the general circulation; (2) releasing-factor and inhibitory-factor neurons, which project axons to the hypophyseal-portal vasculature in the contact zone of the median eminence, through which very high concentrations of these factors (hormones) induce the release of anterior pituitary hormones into the general circulation; and (3) the tuberoinfundibular system and ascending systems (monoamine and other chemically-specific neurons) that modulate the release of releasing and inhibitory factors into the hypophyseal-portal vasculature.





### 12.3 HYPOTHALAMIC NUCLEI

Hypothalamic nuclei and areas are associated with many visceral and neuroendocrine functions. The magnocellular neurons of the PVN and supraoptic nucleus release oxytocin and vasopressin into the posterior pituitary general circulation. PVN parvocellular neurons containing corticotrophin-releasing hormone project to the hypophyseal portal system in the contact zone of the median eminence and induce the release of adrenocorticotrophic hormone (which stimulates the release of cortisol from the adrenal cortex). Descending axons of the PVN also project to the dorsal (motor) nucleus of CN X, the nucleus solitarius, and the intermediolateral cell column preganglionic sympathetic neurons, and regulate preganglionic outflow from the autonomic nervous system. The anterior and posterior areas coordinate parasympathetic and sympathetic outflow, respectively. The dorsomedial (DM) and ventromedial (VM) nuclei and the lateral hypothalamic area regulate appetite, drinking, and reproductive behavior. The preoptic area regulates cyclic neuroendocrine behavior, thermoregulation, and the sleep-wake cycle. The suprachiasmatic nucleus receives visual inputs from the optic tract and regulates circadian rhythms. Several hypothalamic regions are involved in the regulation of sleep.

#### CLINICAL POINT

Hypothalamic nuclei often appear as discrete nuclei and regions that may subserve discrete functions. Early studies of lesions in the hypothalamus led to this impression, resulting in a description of centers, such as the ventromedial nucleus satiety center (lesions led to hyperphagia and obesity) and a lateral appetitive stimulatory center (lesions led to aphagia and cachexia). However, such lesions often damaged passing fiber tracts (e.g., passing axons of the monoaminergic systems) and connections, sometimes even those not associated with the primary functions studied. We now know that many hormones are involved in the control of appetite and food intake. When food is ingested, cholecystokinin and glucagon-like peptide-1 are released by neuroendocrine cells in the intestine, and they act in the brain to suppress appetite and give the sensation of satiety. In the absence of food, these hormone levels are low, permitting appetite and food-seeking behavior. Long-term regulation of food intake also involves the hormone leptin, produced by fat cells. When fat stores are high, leptin is released and acts on the hypothalamus to suppress appetite. When body nutrient stores are depleted, leptin levels are lowered. Other hormones, such as ghrelin, also regulate appetite and eating behavior. Hypothalamic physiology awaits further studies to fully integrate the complex hypothalamic circuitry with the complex hormonal regulation, over which volitional and affective control from higher brain regions is further superimposed. Given the epidemic of obesity in the United States and other “fast-food countries,” a better understanding of the physiology of eating and appetite is urgently needed.

#### CLINICAL POINT

The hypothalamus is a small but complex region of the central nervous system that interconnects the limbic forebrain and the brain stem. The principal functions of the hypothalamus are neuroendocrine regulation, especially through the pituitary gland, and regulation of autonomic function. Thermoregulation is one example of the latter. Several hypothalamic sites, including the anterior and posterior hypothalamic areas, regulate the set point for body temperature within relatively tight parameters. Damage to these mechanisms by head trauma, tumor, surgery, increased intracranial pressure, or vascular problems can induce a change in thermoregulation. Posterior hypothalamic damage is often accompanied by hypothermia, whereas anterior hypothalamic damage is often accompanied by hyperthermia. In addition, inflammatory mediators such as interleukin-1 beta and interleukin-6, whether derived from an infectious process (endotoxin or pyrogen) or from other sources of inflammation, can activate some of the anterior regions of the hypothalamus such as the preoptic area and can induce fever. These inflammatory mediators also can produce classic illness behavior and can powerfully activate both the hypothalamo-pituitary-adrenal axis and the hypothalamo-sympathetic axis, driving a classic stress response. Altered internal body temperature also can be affected by intracranial surgery, susceptibility to some anesthetic agents (malignant hyperthermia), and susceptibility to some neuroleptic drugs.

A major role of the hypothalamus is neuroendocrine regulation of the anterior and posterior pituitary. Neurons in the supraoptic and paraventricular nuclei send axonal connections directly to the posterior pituitary to release oxytocin and vasopressin into the general circulation. Many other collections of neurons, in the hypothalamus and elsewhere, send axonal connections to the hypophyseal-portal vascular system in the contact zone of the median eminence and release releasing factors (hormones) and inhibitory factors (hormones) that regulate the secretion of a variety of hormones from pituicytes in the anterior pituitary. These releasing-factor neurons and inhibitory-factor neurons receive extensive input from brain stem, hypothalamic, and limbic forebrain sources. Some of these neurons (such as the corticotrophin-releasing factor neurons in the PVN) also receive input from chemical sources, such as interleukin-1 beta, prostaglandin E<sub>2</sub>, and nitric oxide. Interleukin-1 beta, both directly and indirectly, can drive the response of corticotrophin-releasing factor, thereby activating the hypothalamo-pituitary-adrenal system to stimulate cortisol production and drive the hypothalamo-sympathetic system to stimulate the release of catecholamines. Some neurotransmitters in these releasing-factor neurons and inhibitory-factor neurons can be influenced pharmacologically. Dopamine in the arcuate nucleus acts as a prolactin-inhibitory factor. A dopamine agonist can suppress prolactin output by a prolactin-secreting pituitary tumor (chromophobe adenoma).

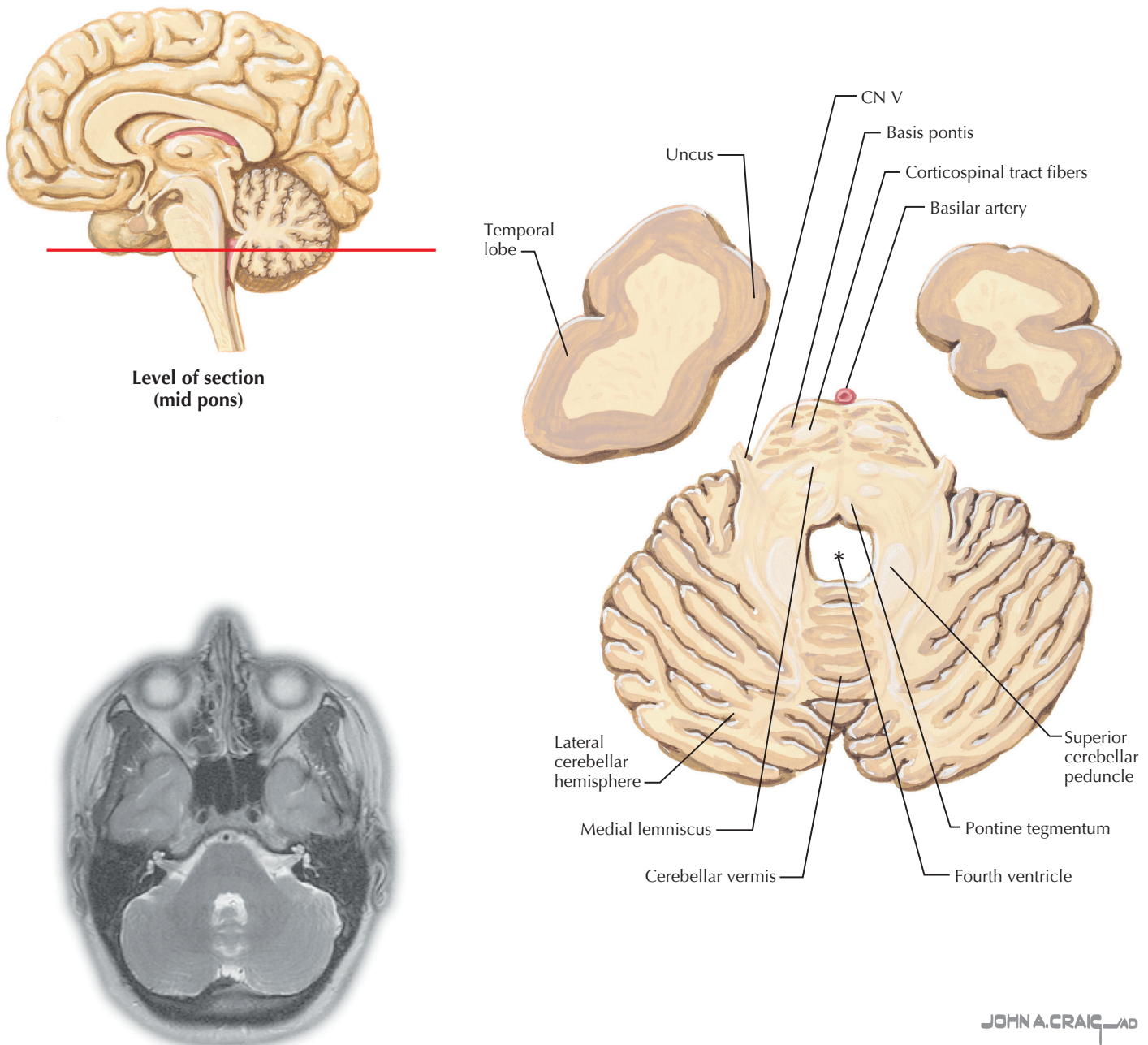


# 13

## TELENCEPHALON

- 13.1A, B** Axial (Horizontal) Sections Through the Forebrain: Level 1—Mid Pons
- 13.2A, B** Axial (Horizontal) Sections Through the Forebrain: Level 2—Rostral Pons
- 13.3A, B** Axial (Horizontal) Sections Through the Forebrain: Level 3—Midbrain
- 13.4A, B** Axial (Horizontal) Sections Through the Forebrain: Level 4—Rostral Midbrain and Hypothalamus
- 13.5A, B** Axial (Horizontal) Sections Through the Forebrain: Level 5—Anterior Commissure and Caudal Thalamus
- 13.6A, B** Axial (Horizontal) Sections Through the Forebrain: Level 6—Head of Caudate and Midthalamus
- 13.7A, B** Axial (Horizontal) Sections Through the Forebrain: Level 7—Basal Ganglia and Internal Capsule
- 13.8A, B** Axial (Horizontal) Sections Through the Forebrain: Level 8—Dorsal Caudate, Splenium, and Genu of Corpus Callosum
- 13.9A, B** Axial (Horizontal) Sections Through the Forebrain: Level 9—Body of Corpus Callosum
- 13.10A, B** Axial (Horizontal) Sections Through the Forebrain: Level 10—Centrum Semiovale
- 13.11A, B** Coronal Sections Through the Forebrain: Level 1—Genu of Corpus Callosum
- 13.12A, B** Coronal Sections Through the Forebrain: Level 2—Head of Caudate Nucleus/Nucleus Accumbens
- 13.13A, B** Coronal Sections Through the Forebrain: Level 3—Anterior Commissure/Columns of Fornix
- 13.14A, B** Coronal Sections Through the Forebrain: Level 4—Amygdala, Anterior Limb of Internal Capsule
- 13.15A, B** Coronal Sections Through the Forebrain: Level 5—Mammillary Body
- 13.16A, B** Coronal Sections Through the Forebrain: Level 6—Mammillothalamic Tract/Substantia Nigra, Rostral Hippocampus
- 13.17A, B** Coronal Sections Through the Forebrain: Level 7—Midthalamus
- 13.18A, B** Coronal Sections Through the Forebrain: Level 8—Geniculate Nuclei
- 13.19A, B** Coronal Sections Through the Forebrain: Level 9—Caudal Pulvinar and Superior Colliculus
- 13.20A, B** Coronal Sections Through the Forebrain: Level 10—Splenium of Corpus Callosum
- 13.21** Layers of the Cerebral Cortex
- 13.22** Cortical Neuronal Cell Types
- 13.23** Vertical Columns: Functional Units of the Cerebral Cortex
- 13.24** Efferent Connections of the Cerebral Cortex
- 13.25** Neuronal Origins of Efferent Connections of the Cerebral Cortex
- 13.26** Cortical Association Pathways
- 13.27** Major Cortical Association Bundles
- 13.28** Color Imaging of Association Pathways
- 13.29** Color Imaging of Projection Pathways from the Cerebral Cortex
- 13.30** Functional Magnetic Resonance Imaging
- 13.31** Aphasias and Cortical Areas of Damage
- 13.32** Noradrenergic Pathways
- 13.33** Serotonergic Pathways
- 13.34** Dopaminergic Pathways
- 13.35** Central Cholinergic Pathways
- 13.36** Distribution of Pathology in the Brain in Alzheimer Disease
- 13.37** The Olfactory Nerve and Nerves of the Nose

## Level 1: Mid Pons

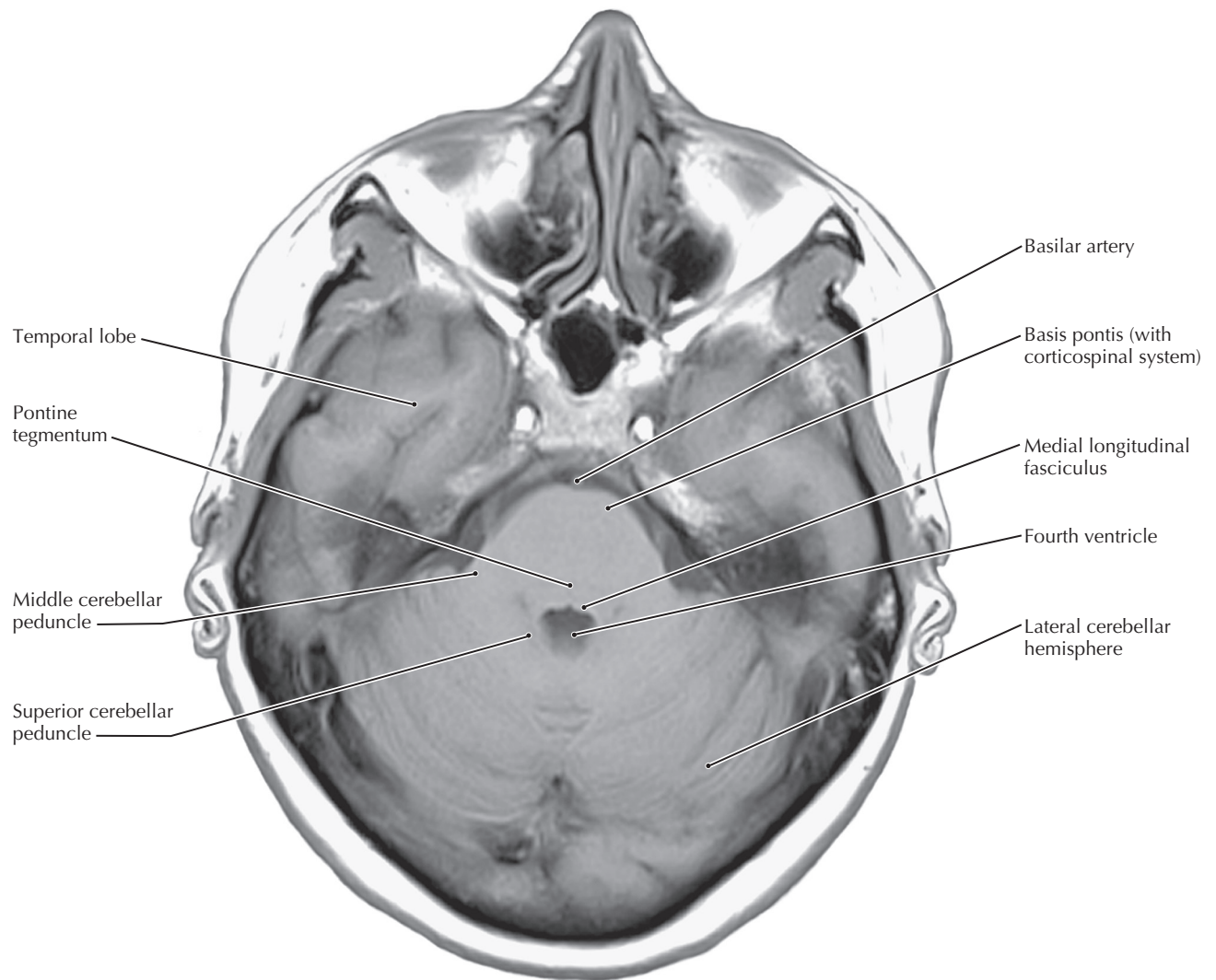
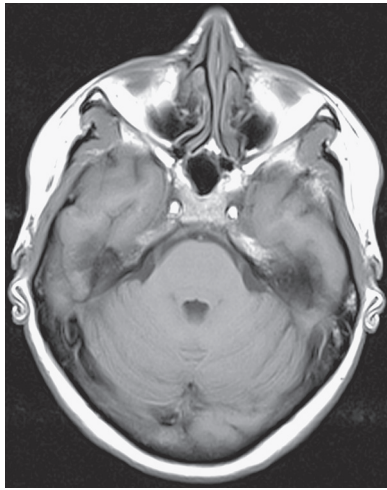


JOHN A. CRAIG, MD

### 13.1A AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 1—MID PONS

These axial (horizontal) sections compare anatomical sections and high-resolution magnetic resonance (MR) images. They are cut in the true horizontal (axial) plane, not in the older 25-degree tilt. The most important anatomical relationships in these sections center on the internal capsule (IC). The head of the caudate nucleus is medial to the anterior limb of the IC and forms the lateral margin of the frontal pole of the lateral ventricle. The thalamus is medial to the posterior limb of the IC. The globus pallidus and putamen are lateral to the wedge-

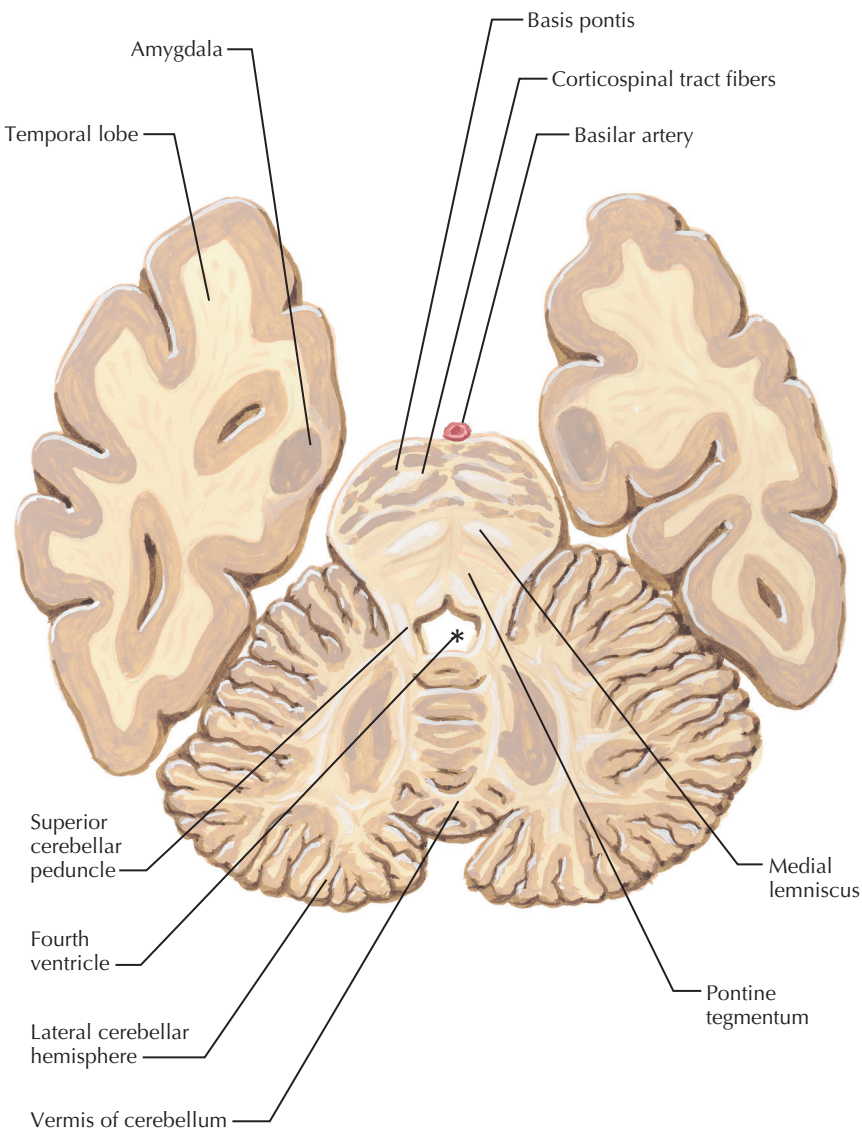
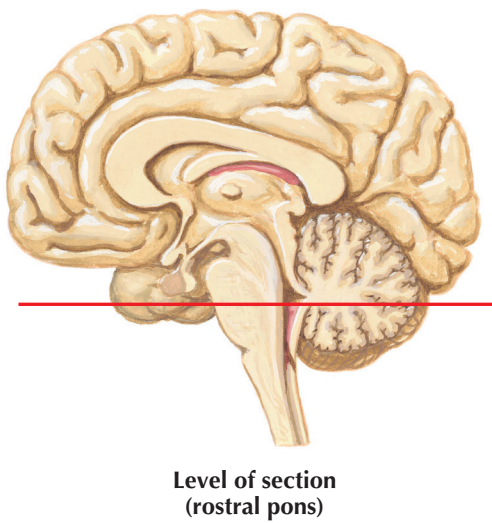
shaped IC. The posterior limb of the IC carries the major descending corticospinal, corticorubral, and corticoreticular fibers and the ascending sensory fibers of the somatosensory and trigeminal systems. The most posterior portions of the posterior limb also carry the auditory and visual projections to their respective cortices. The genu of the IC carries the corticobulbar fibers. The anterior limb of the IC carries cortical projections to the striatum and the pontine nuclei (pontocerebellar system). The full-plate MR images are T1-weighted; the ventricles appear dark. The scout MRI images that accompany the drawings are T2-weighted MR images, in which the CSF appears white.



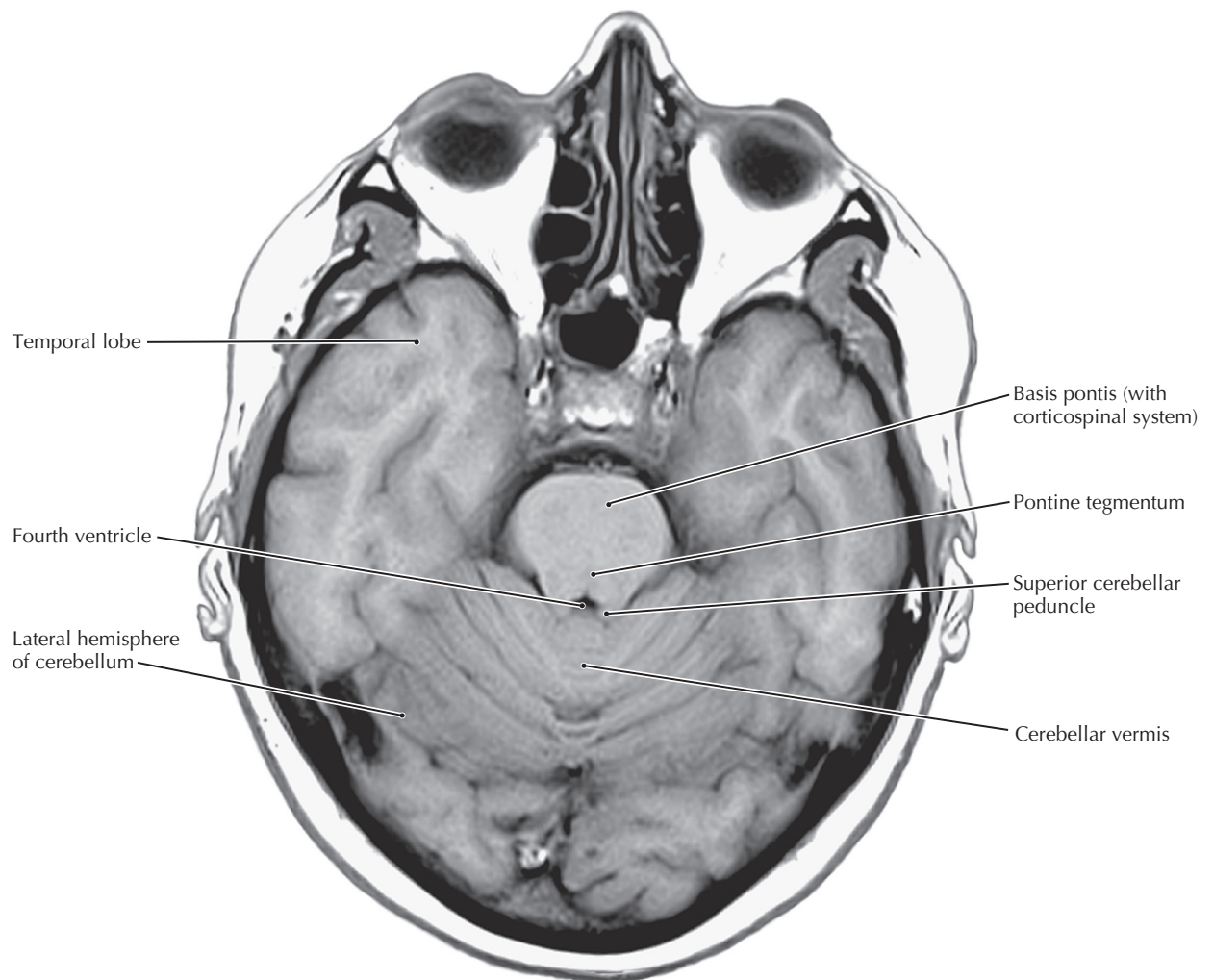
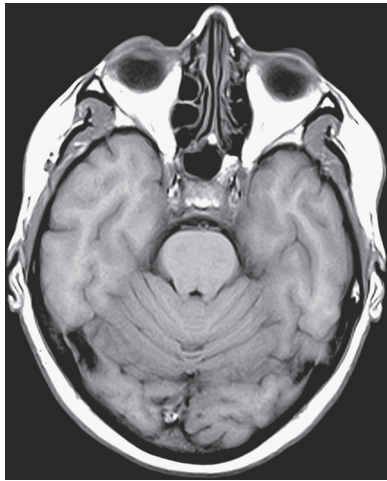
**13.1B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 1—MID PONS**



Level 2: Rostral Pons

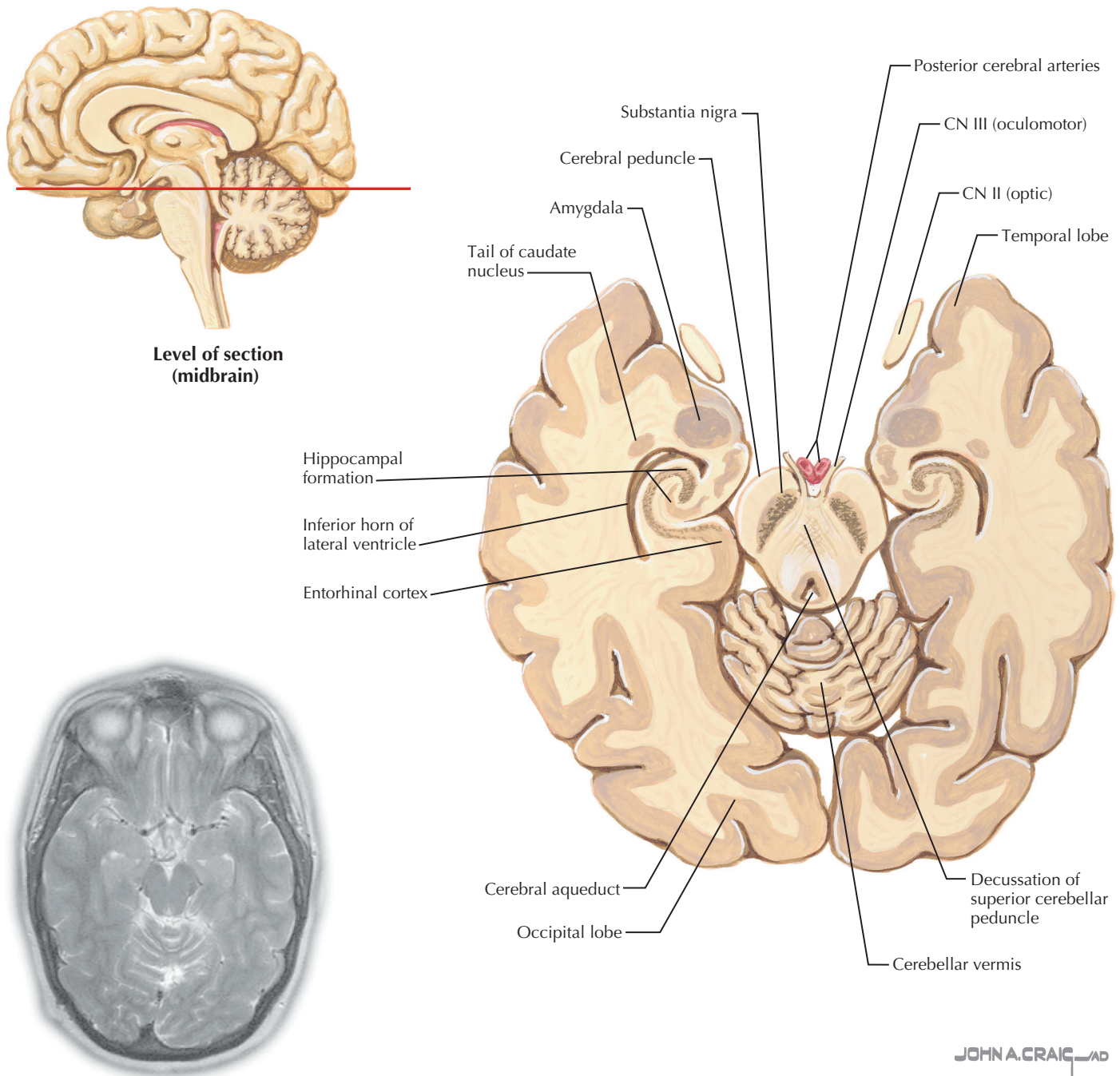


JOHN A. CRAIG MD



**13.2B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 2—ROSTRAL PONS (CONTINUED)**

## Level 3: Midbrain



### 13.3A AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 3—MIDBRAIN

#### CLINICAL POINT

The temporal lobe includes the amygdaloid nuclei, the hippocampal formation and associated cortex, the transverse gyrus of Heschl, some language-associated cortical regions (Wernicke's area in the dominant hemisphere), Meyer's loop of geniculocalcarine axons, the inferior

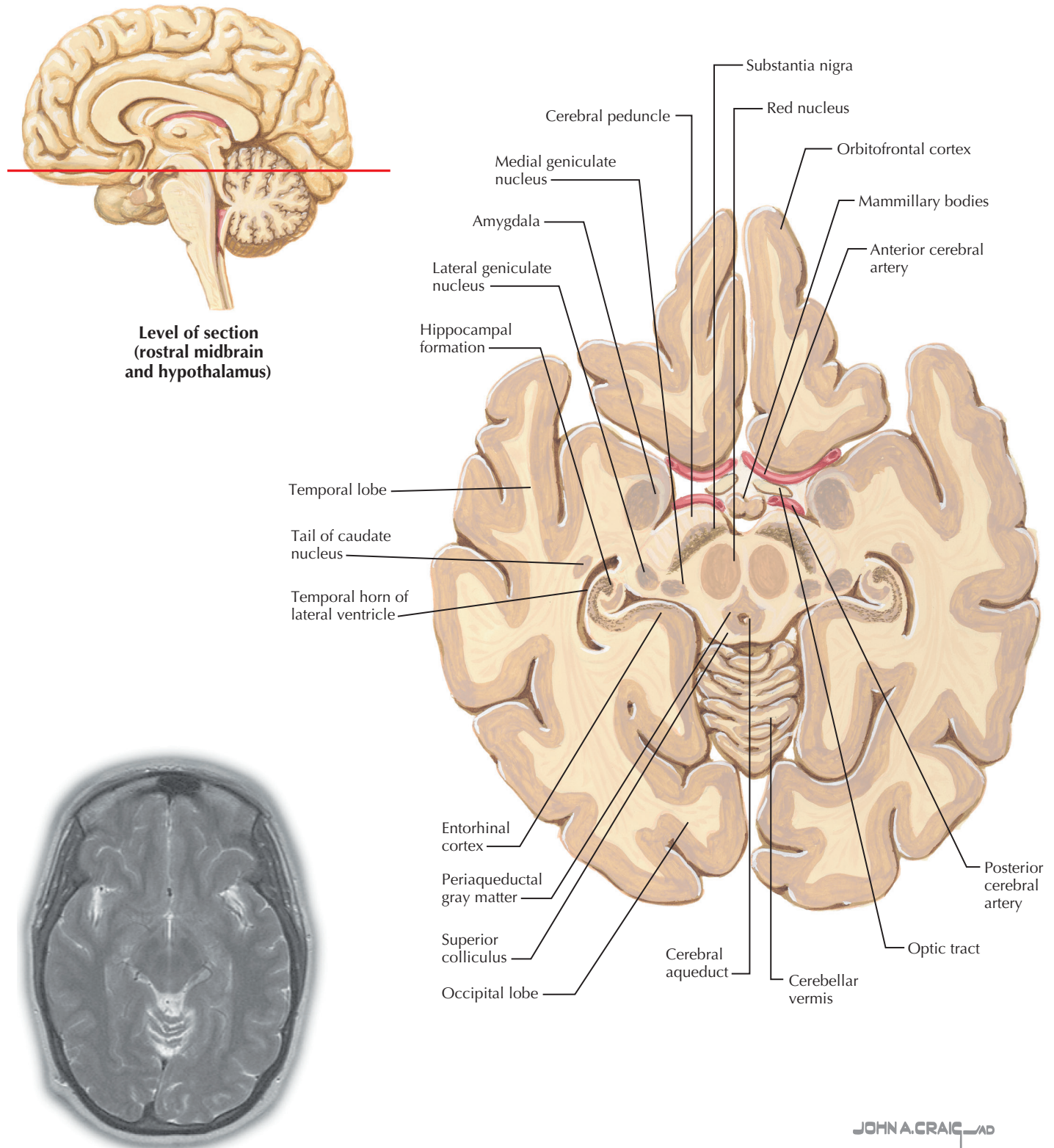
horn of the lateral ventricle, and extensive cortical areas (superior, middle, and inferior temporal gyri). The temporal lobe can be damaged by trauma, infarcts, tumors, abscesses, and other pathological conditions. Such damage can result in auditory hallucinations, delirium and psychotic behavior, sometimes a contralateral upper quadrantanopia (if Meyer's loop is damaged), and receptive aphasia (Wernicke's aphasia) that involves a lack of understanding of verbal information (in a lesion of the dominant hemisphere). Some very specific lesions in the temporal lobe result in an agnosia for recognition of faces (prosopagnosia).



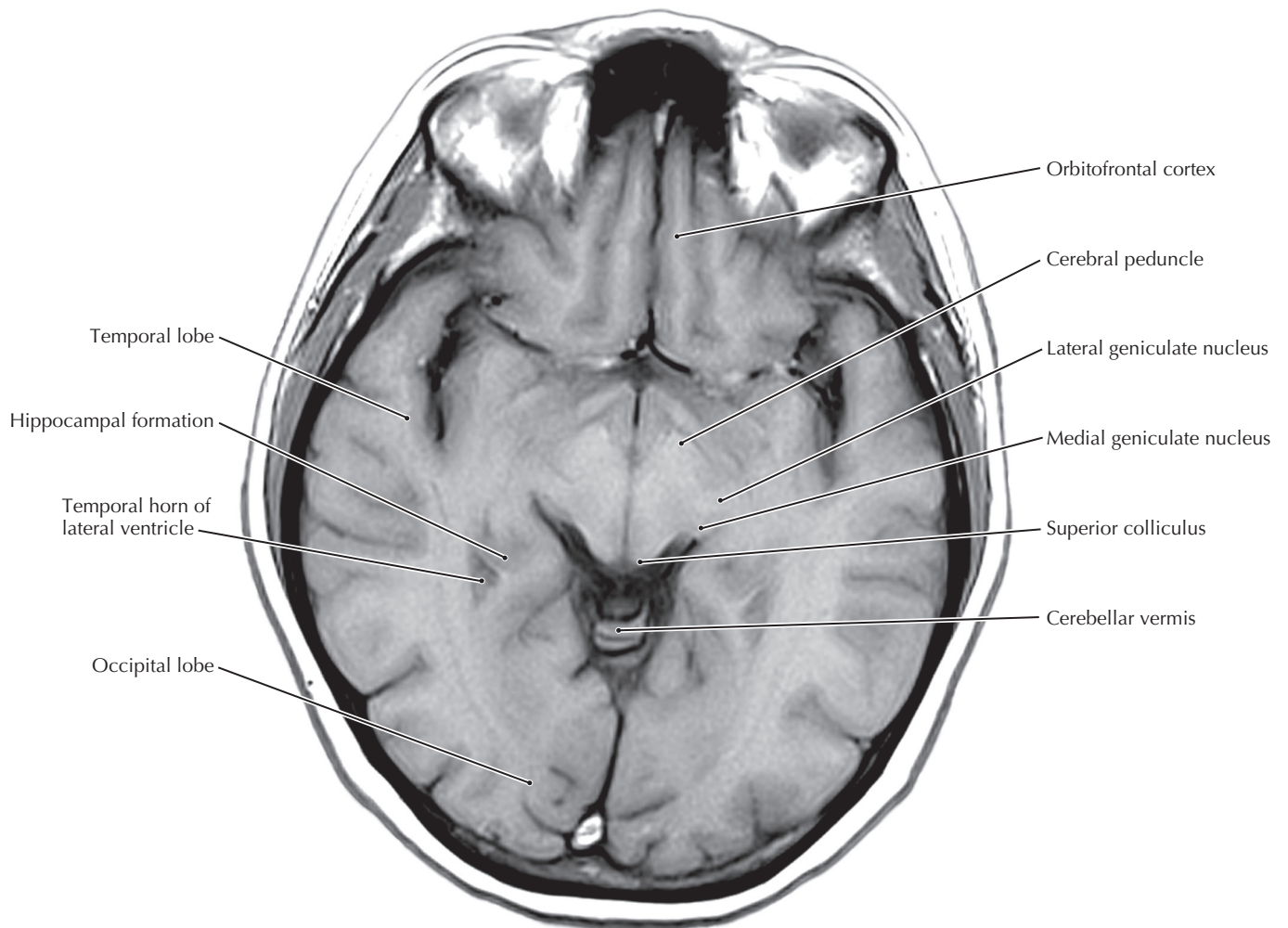
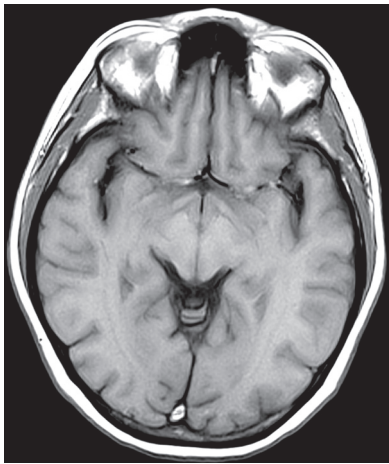


**13.3B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 3—MIDBRAIN (CONTINUED)**

### Level 4: Rostral Midbrain and Hypothalamus



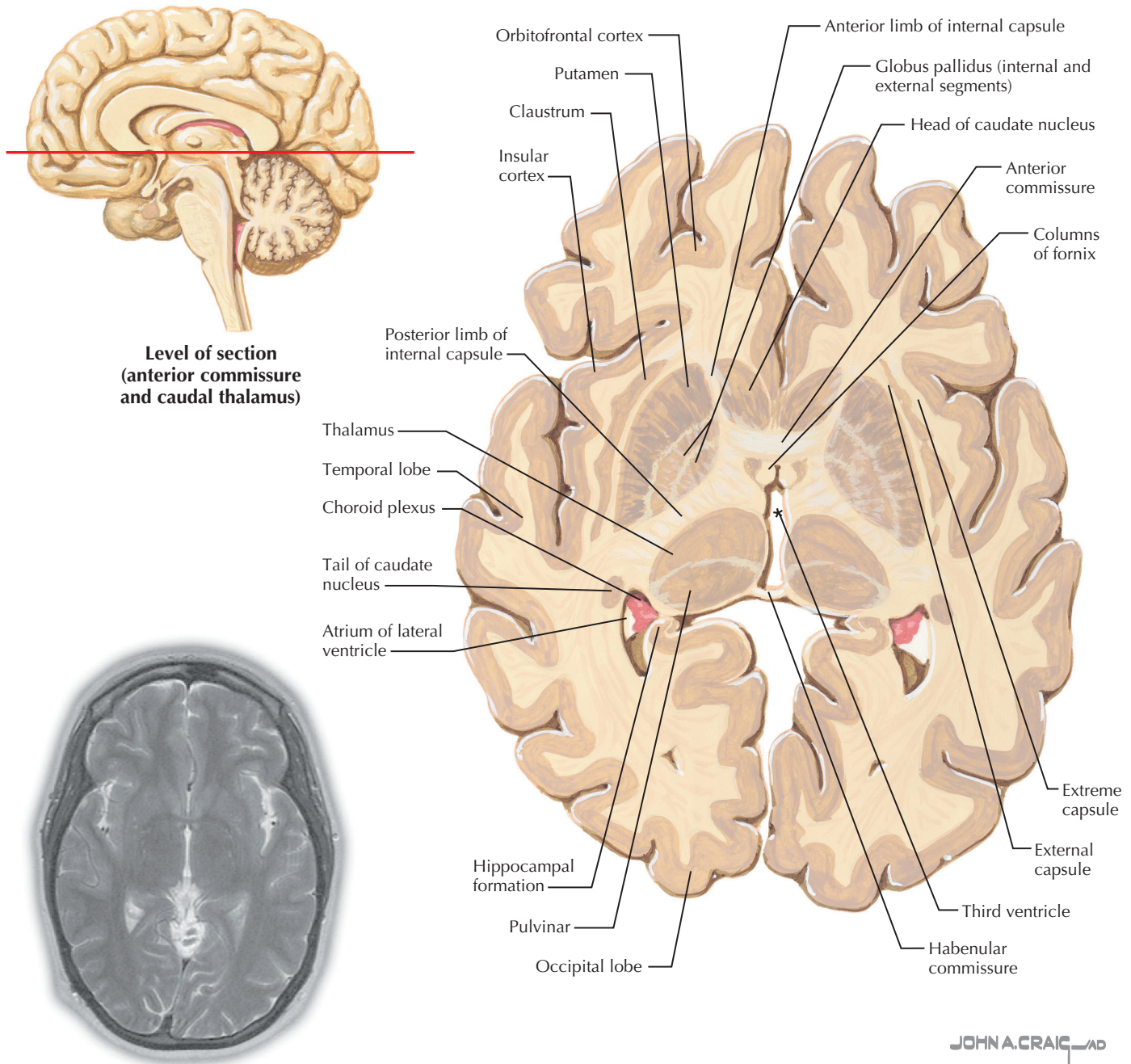
JOHN A. CRAIG MD



**13.4B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 4—ROSTRAL MIDBRAIN AND HYPOTHALAMUS (CONTINUED)**



## Level 5: Anterior Commissure and Caudal Thalamus



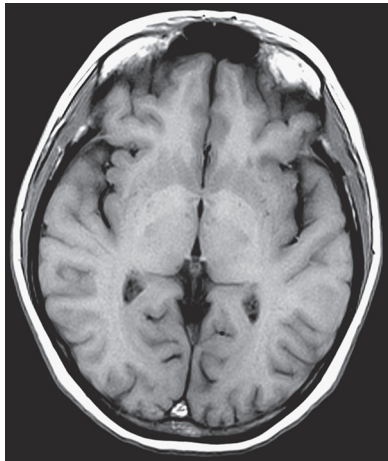
JOHN A. CRAIG MD

### 13.5A AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 5—ANTERIOR COMMISSURE AND CAUDAL THALAMUS

#### CLINICAL POINT

The basal ganglia assist the cerebral cortex in planning and generating desired programs of activity and suppressing undesired programs of activity. The most conspicuous arena in which these functions are observed is motor activity. Basal ganglia disorders produce movement problems that are often involuntary in nature and are commonly accompanied by cognitive and affective symptoms (e.g., Huntington's disease). The principal route of information flow from the basal ganglia is from the thalamus and cerebral cortex to the striatum

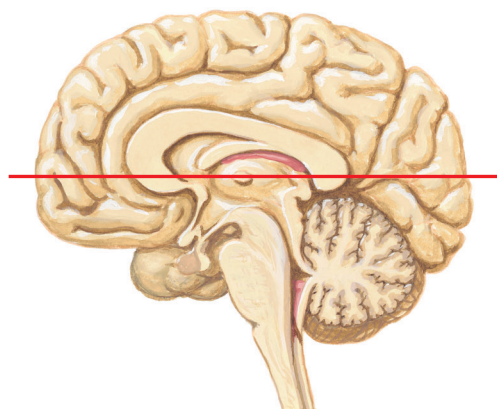
(caudate nucleus and putamen), then to the globus pallidus, then back to the thalamus and cortex, completing the loop. Disruption of this loop can produce excessive movements (e.g., choreiform and athetoid movements, tremor) or diminished movements (bradykinesia). In some instances, specific nuclei are known to be associated with such changes. A small lacunar infarct in the subthalamic nucleus results in wild, flinging (ballistic) movements in the contralateral limbs. However, a surgical lesion in the subthalamic nucleus may ameliorate some of the movement problems seen in Parkinson's disease. The subthalamus most likely drives activity in the internal segment of the globus pallidus, which in turn can be modified by the external segment. A pathological lesion in the globus pallidus can produce rigidity and akinesia; a surgical pallidal lesion may reduce excessive movements in other basal ganglia disorders.



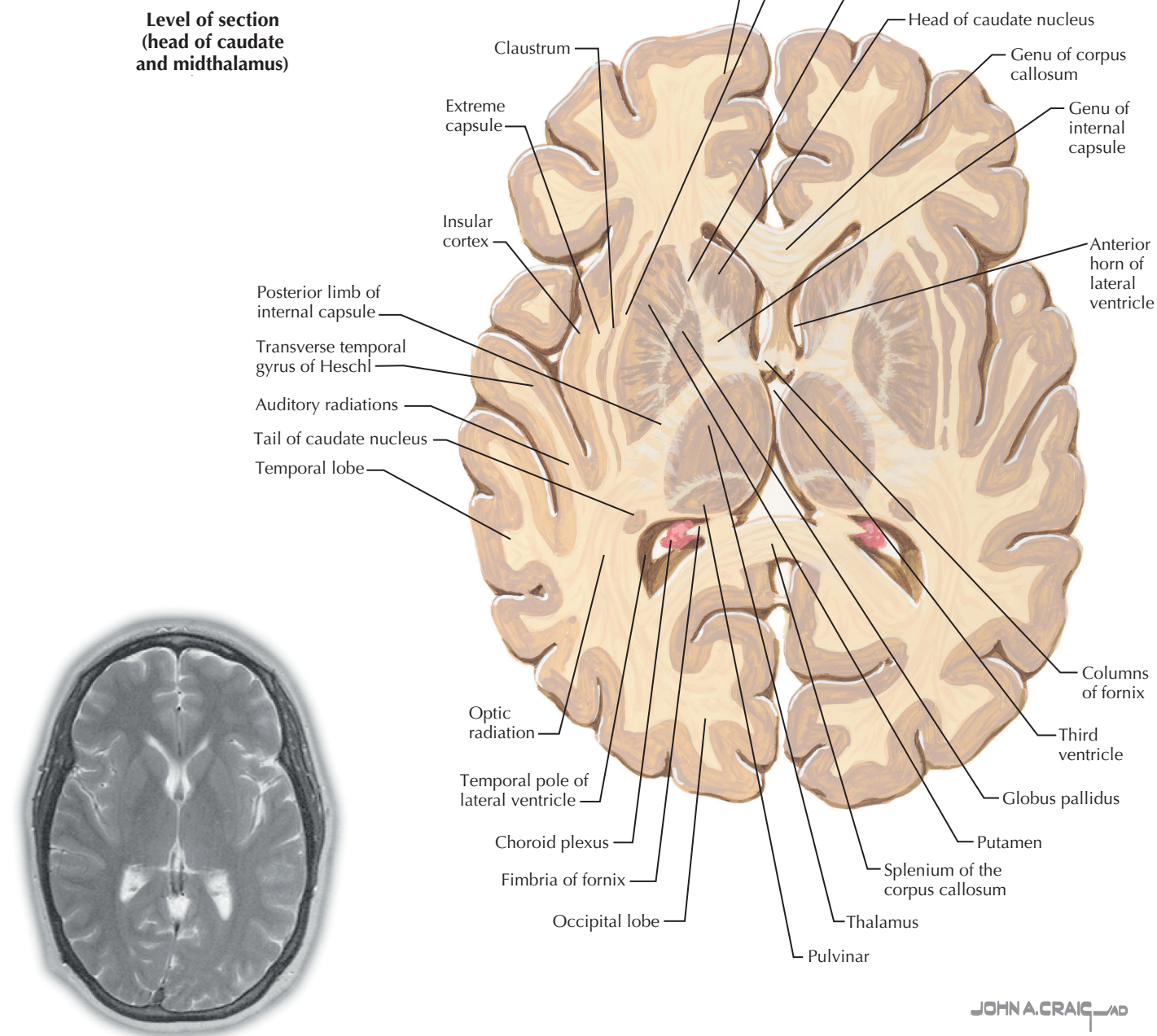
**13.5B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 5—ANTERIOR COMMISSURE AND CAUDAL THALAMUS (CONTINUED)**



## Level 6: Head of Caudate and Midthalamus

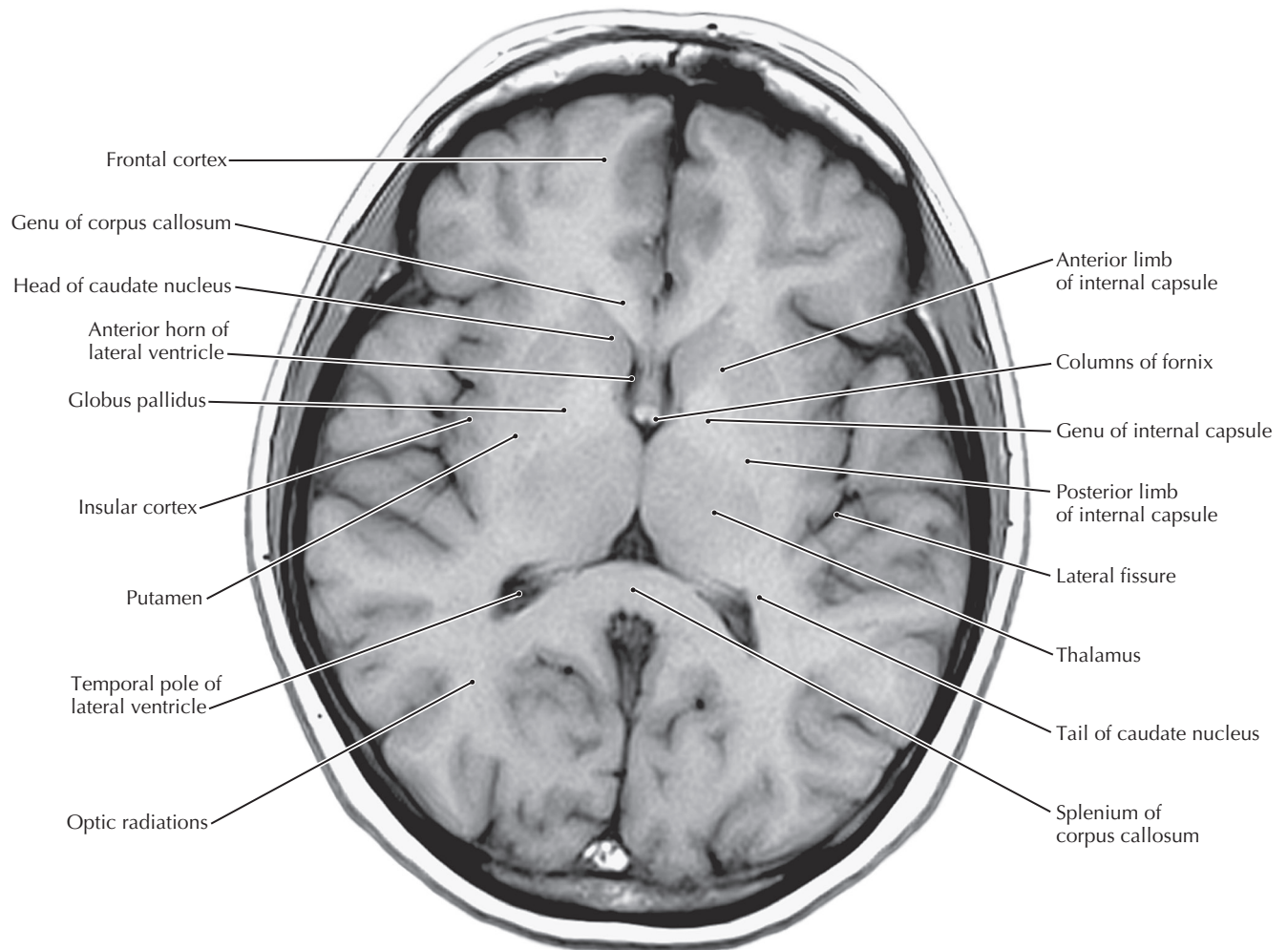
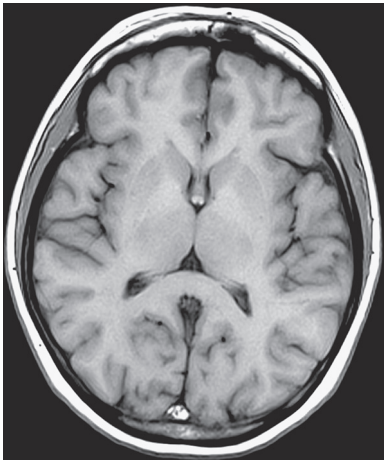


Level of section  
(head of caudate  
and midthalamus)



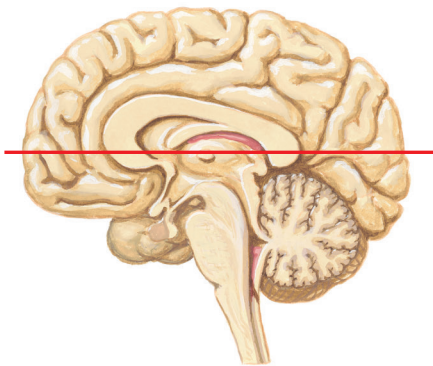
JOHN A. CRAIG, MD



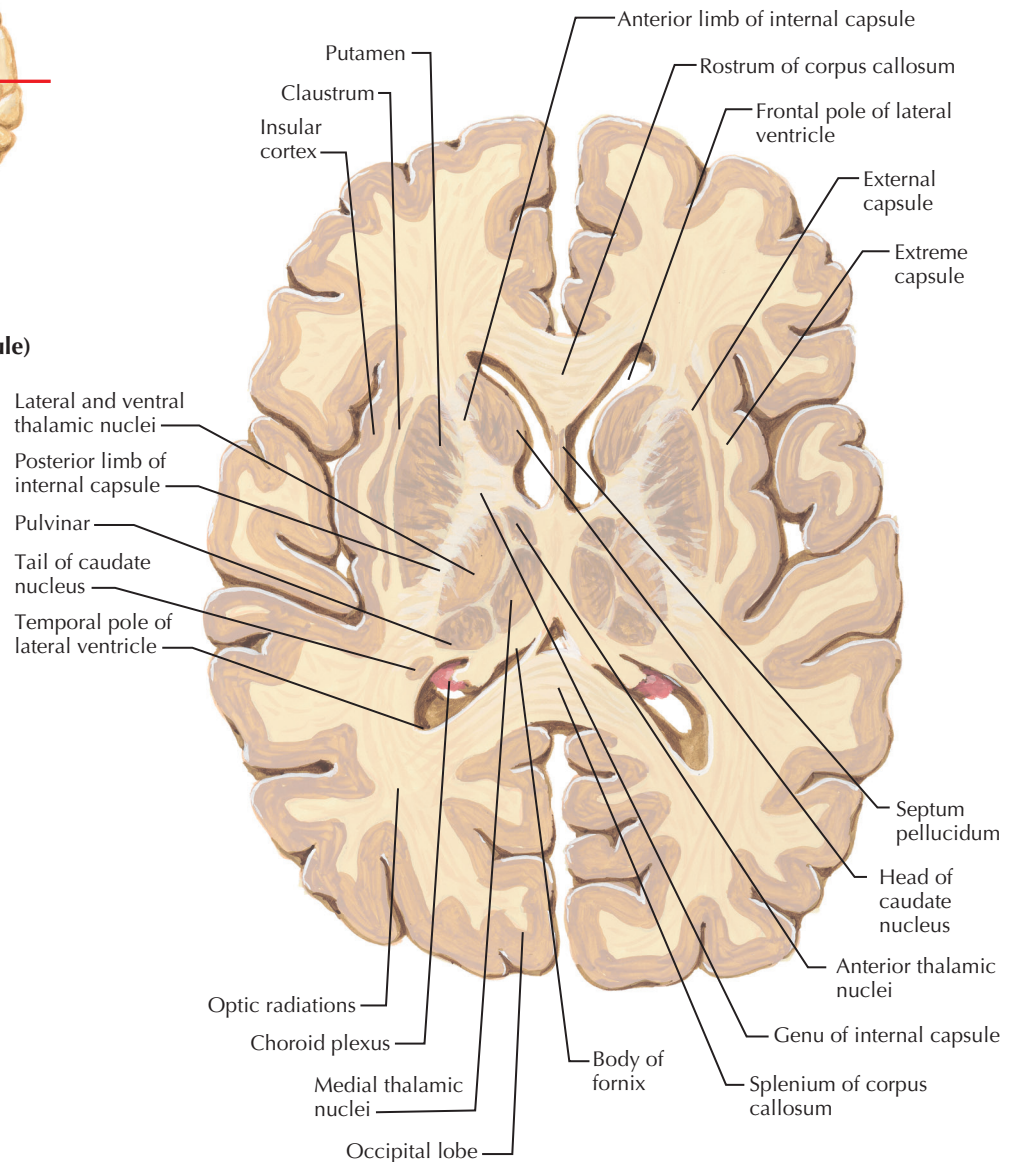


**13.6B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 6—HEAD OF CAUDATE AND MIDTHALAMUS (CONTINUED)**

## Level 7: Basal Ganglia and Internal Capsule



Level of section  
(basal ganglia and internal capsule)



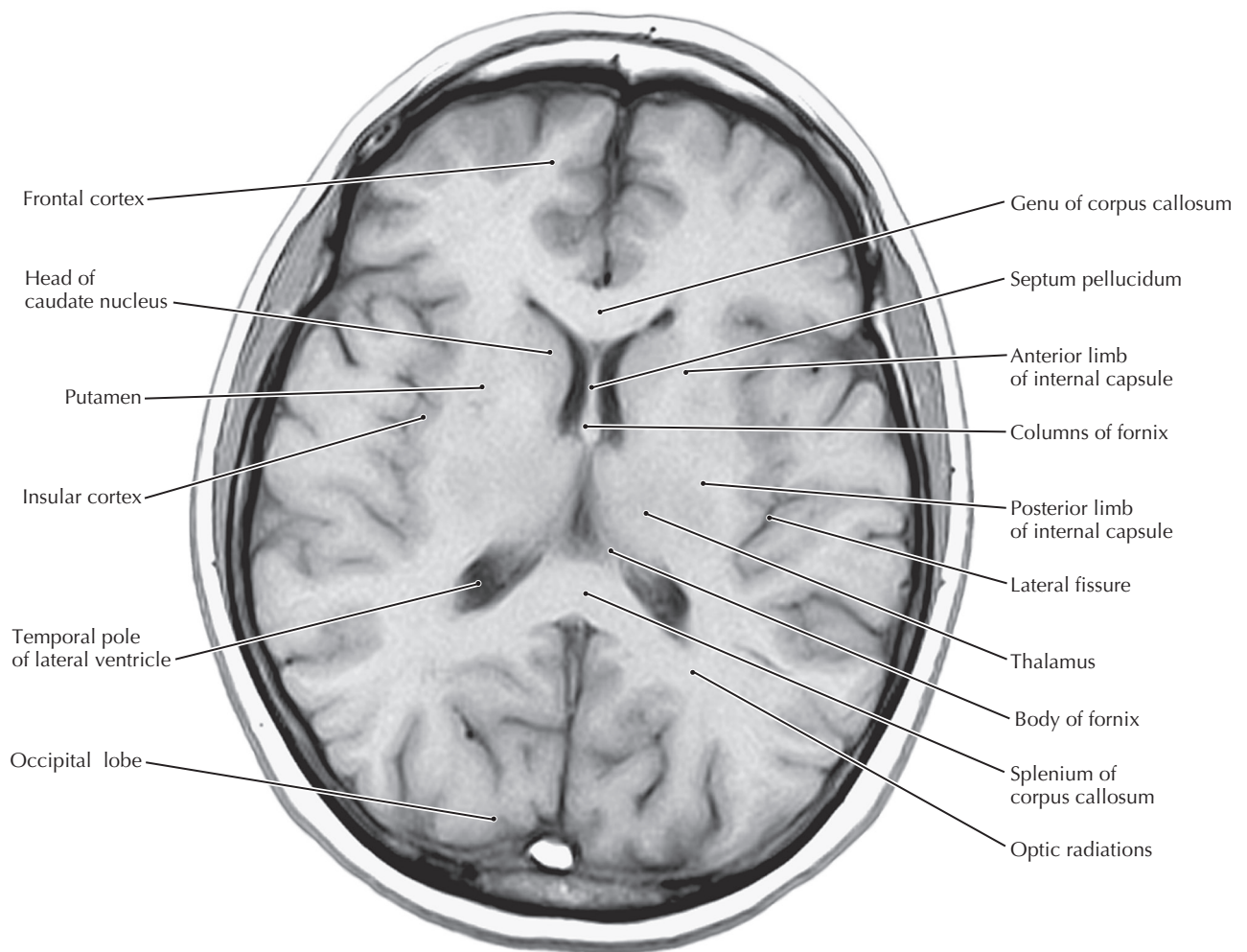
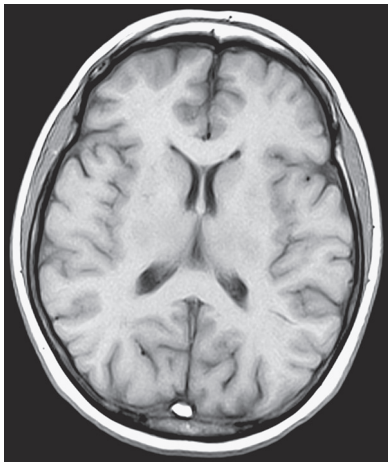
JOHN A. CRAIG AD

### 13.7A AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 7—BASAL GANGLIA AND INTERNAL CAPSULE

#### CLINICAL POINT

Huntington's disease is an autosomal dominant disorder caused by a trinucleotide repeat (CAG) on the short arm of chromosome 4. It results in a progressive, untreatable disease that includes a movement disorder (choreiform movements: brisk, jerky, forcible, arrhythmic movements), progressive cognitive impairment, and affective disor-

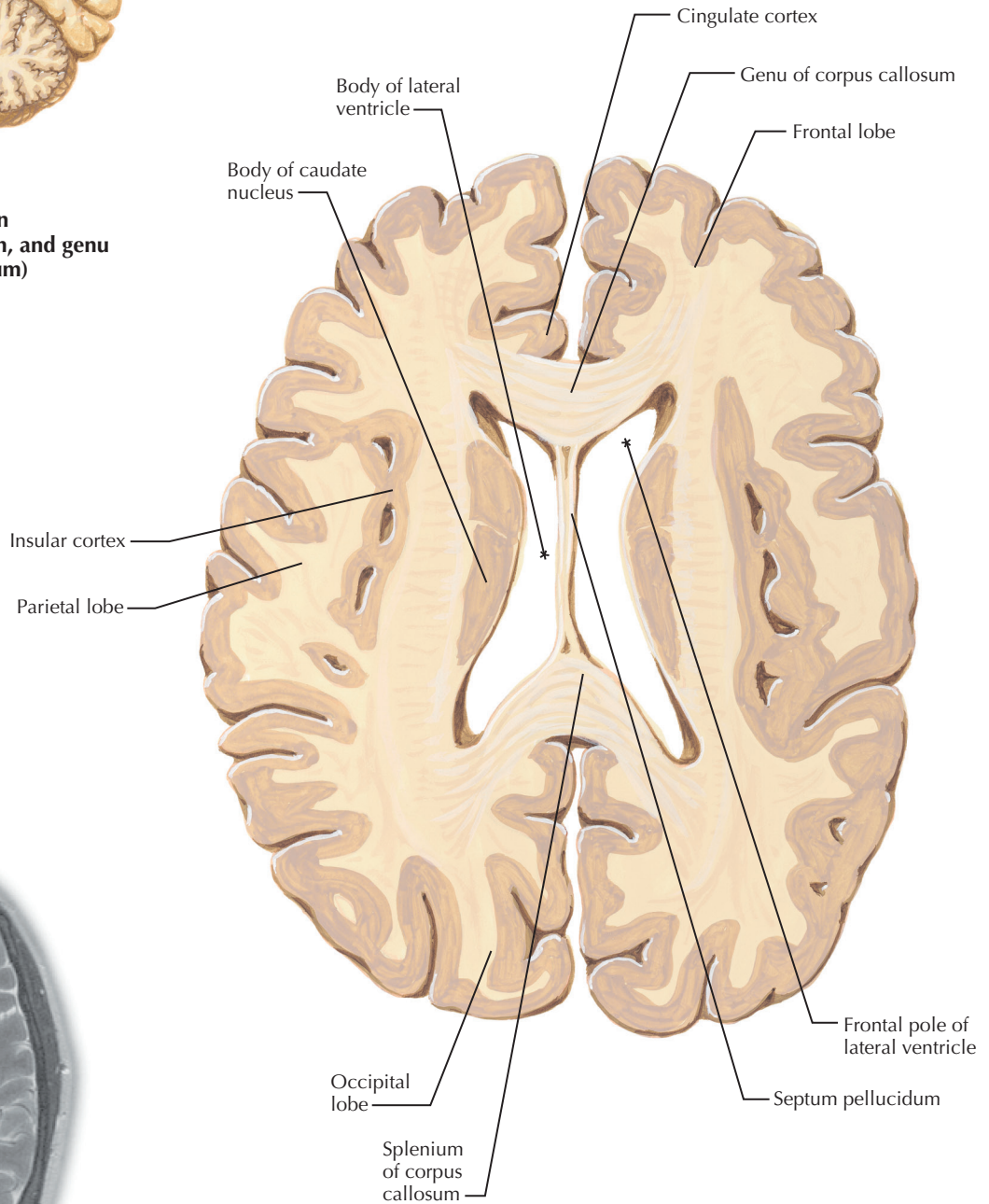
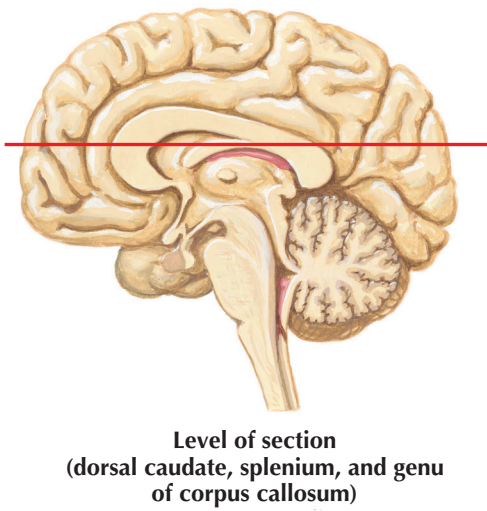
ders (such as depression, psychotic behavior). This disease progresses from a state of minor impairment (clumsiness) with minor behavioral problems (irritability and depression) to major impairment, dementia, and a decline that leads to incapacitation and ultimately to an early death. The anatomical hallmark of this disease is marked degeneration of the caudate nucleus (also the putamen). The characteristic bulge of the head of the caudate into the frontal pole of the lateral ventricle is lost. Most of the medium spiny caudate neurons that project to the globus pallidus degenerate as the result of damage from excess  $\text{Ca}^{++}$  influx caused by glutamate excitotoxic damage via activation of the *N*-methyl-D-aspartate (NMDA) receptors. The intrinsic cholinergic interneurons of the striatum also degenerate in Huntington's disease.



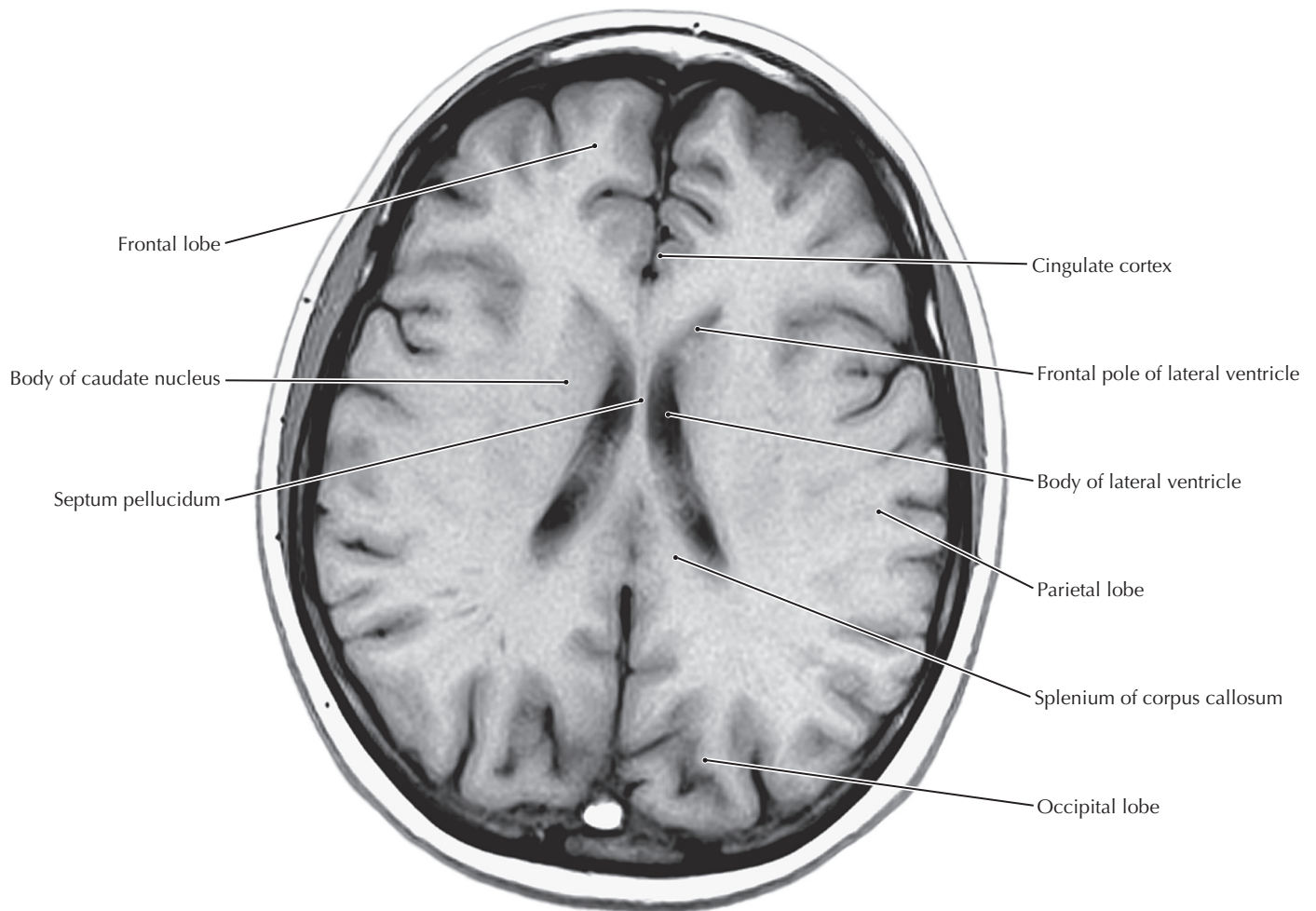
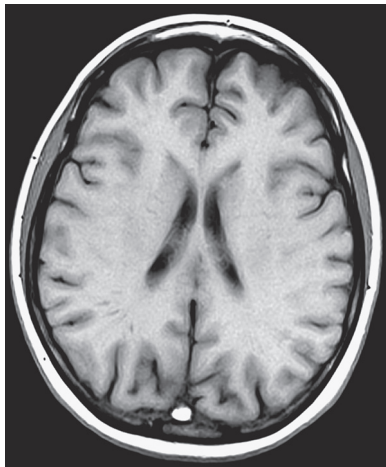
**13.7B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 7—BASAL GANGLIA AND INTERNAL CAPSULE (CONTINUED)**



Level 8: Dorsal Caudate, Splenium, and Genu of Corpus Callosum

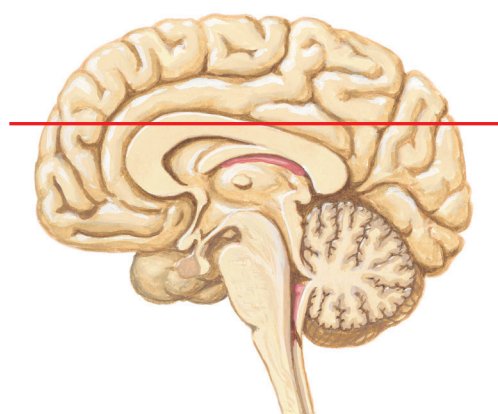


JOHN A. CRAIG, MD

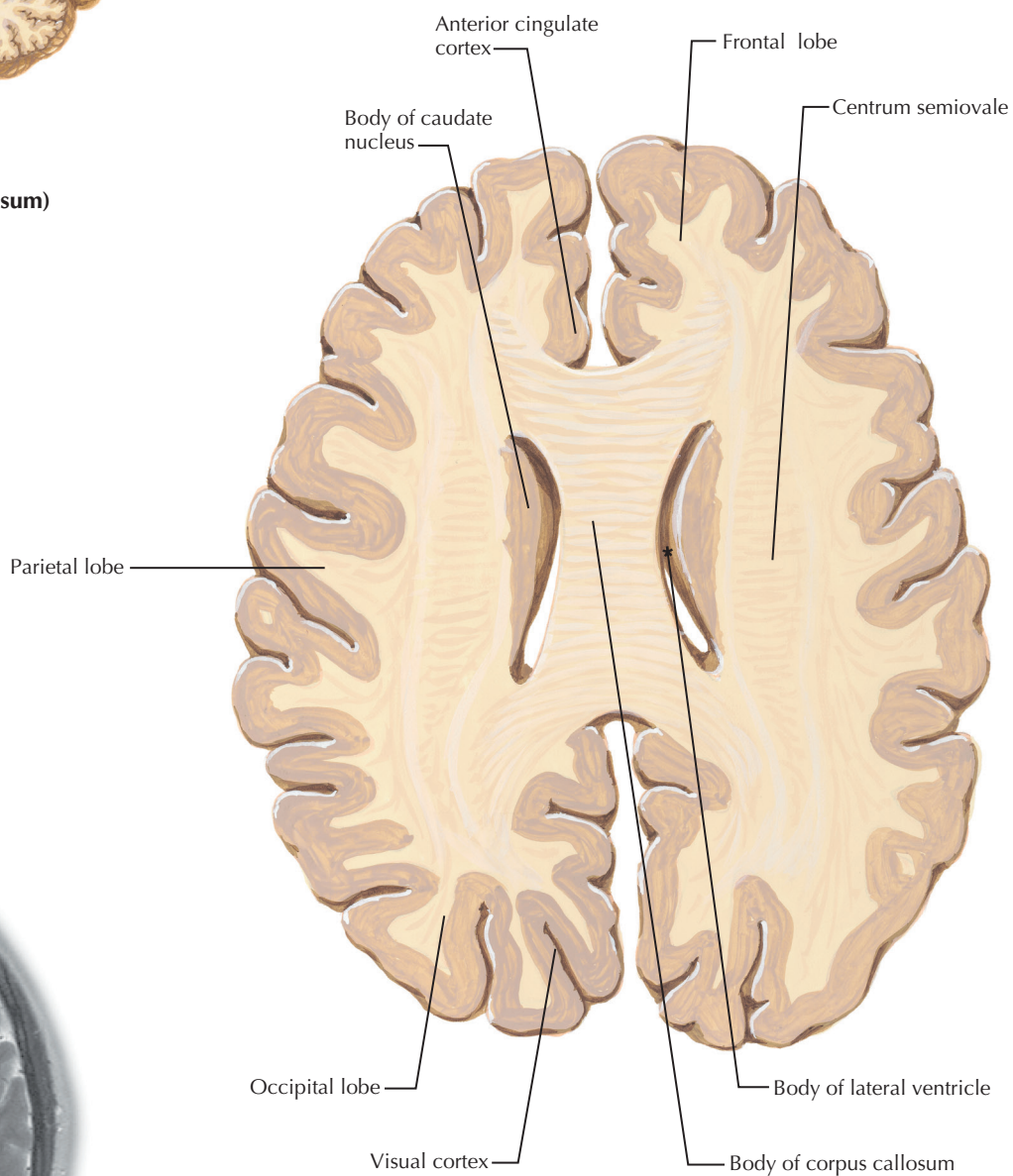


**13.8B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 8—DORSAL CAUDATE, SPLENIUM, AND GENU OF CORPUS CALLOSUM (CONTINUED)**

### Level 9: Body of Corpus Callosum

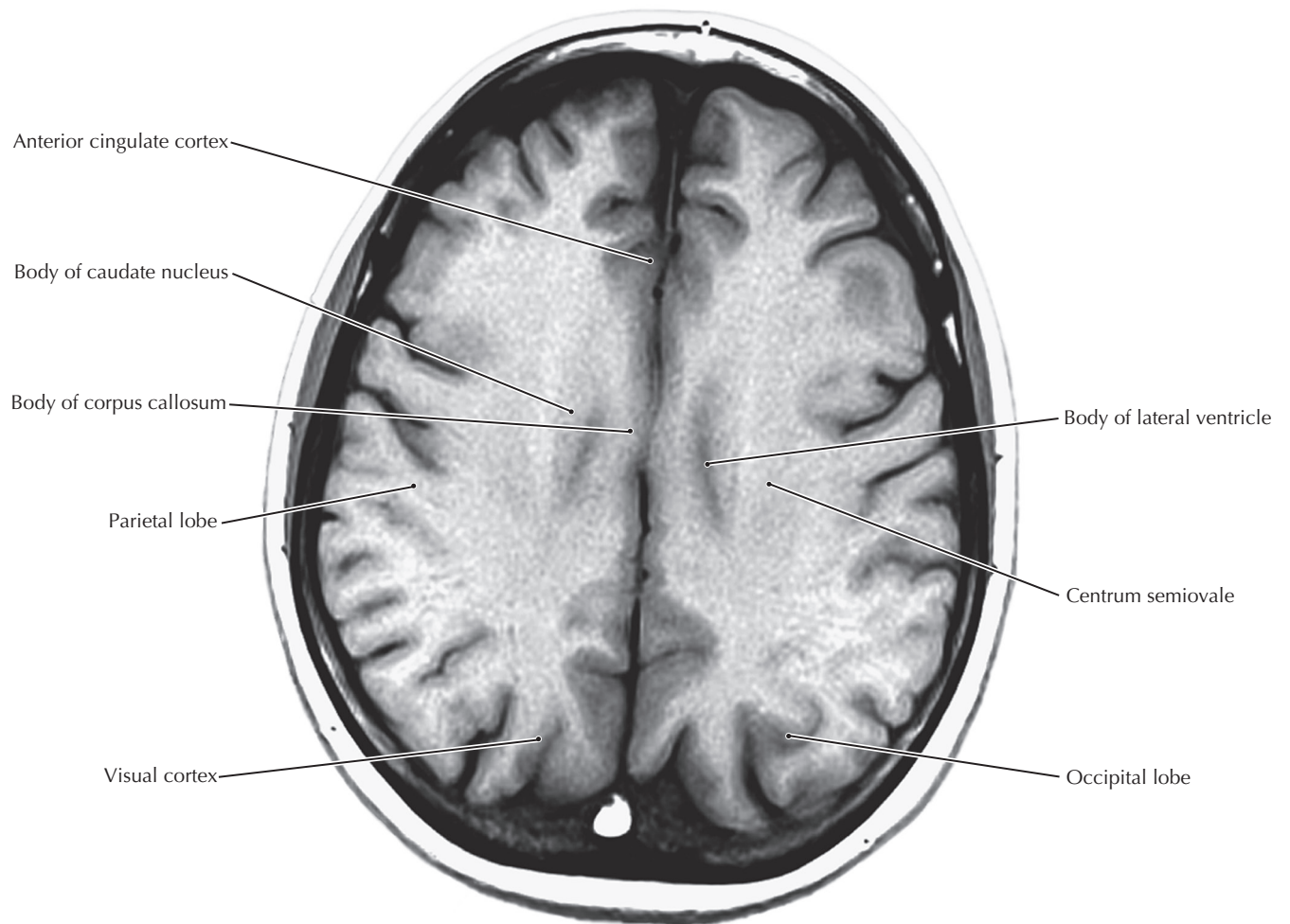
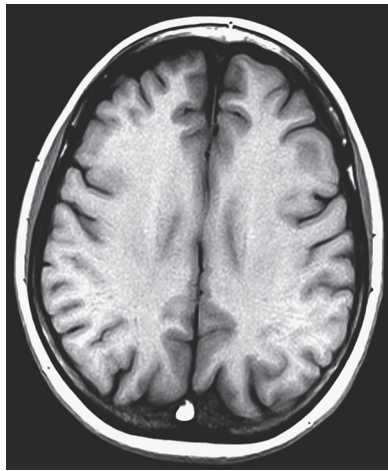


Level of section  
(body of corpus callosum)



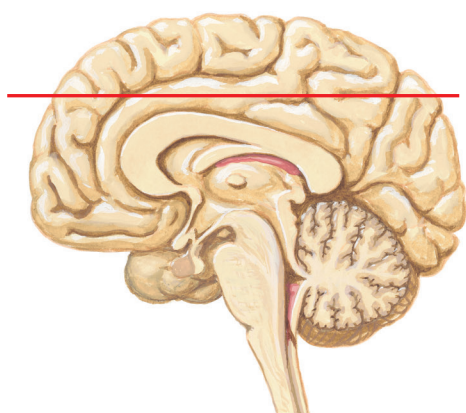
JOHN A. CRAIG MD



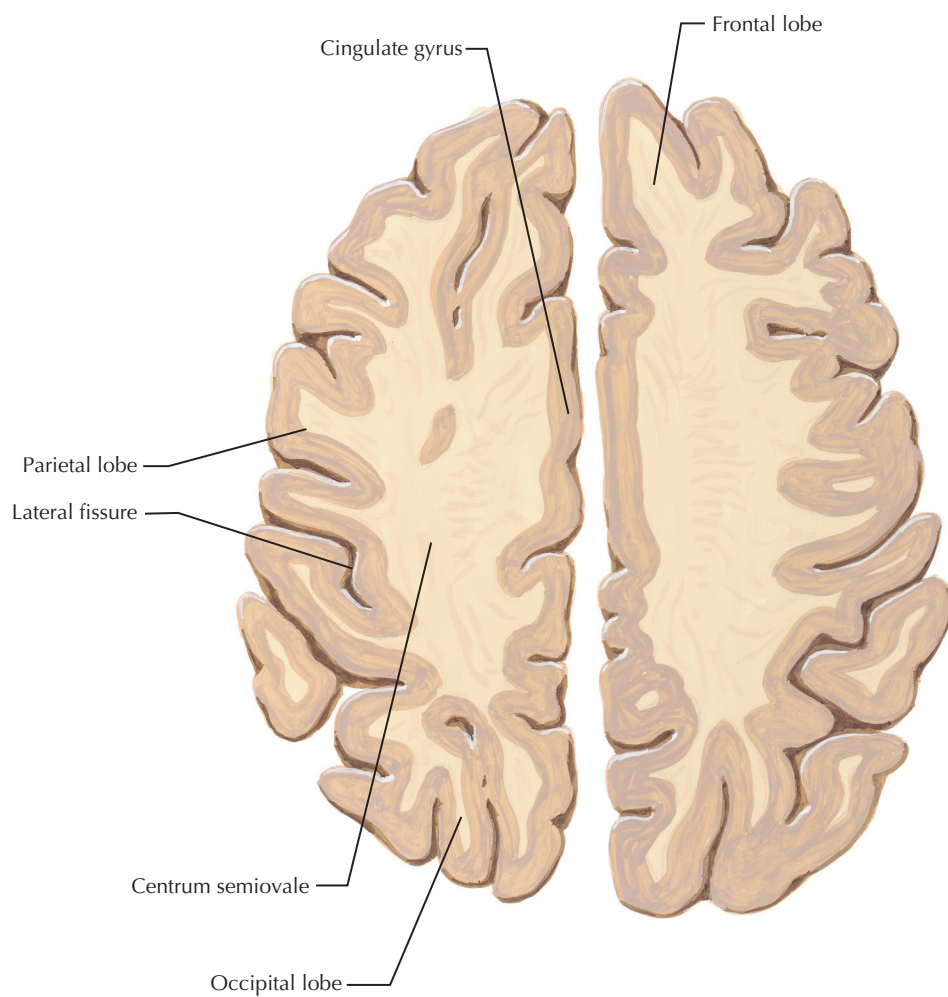


**13.9B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 9—BODY OF CORPUS CALLOSUM (CONTINUED)**

### Level 10: Centrum Semiovale



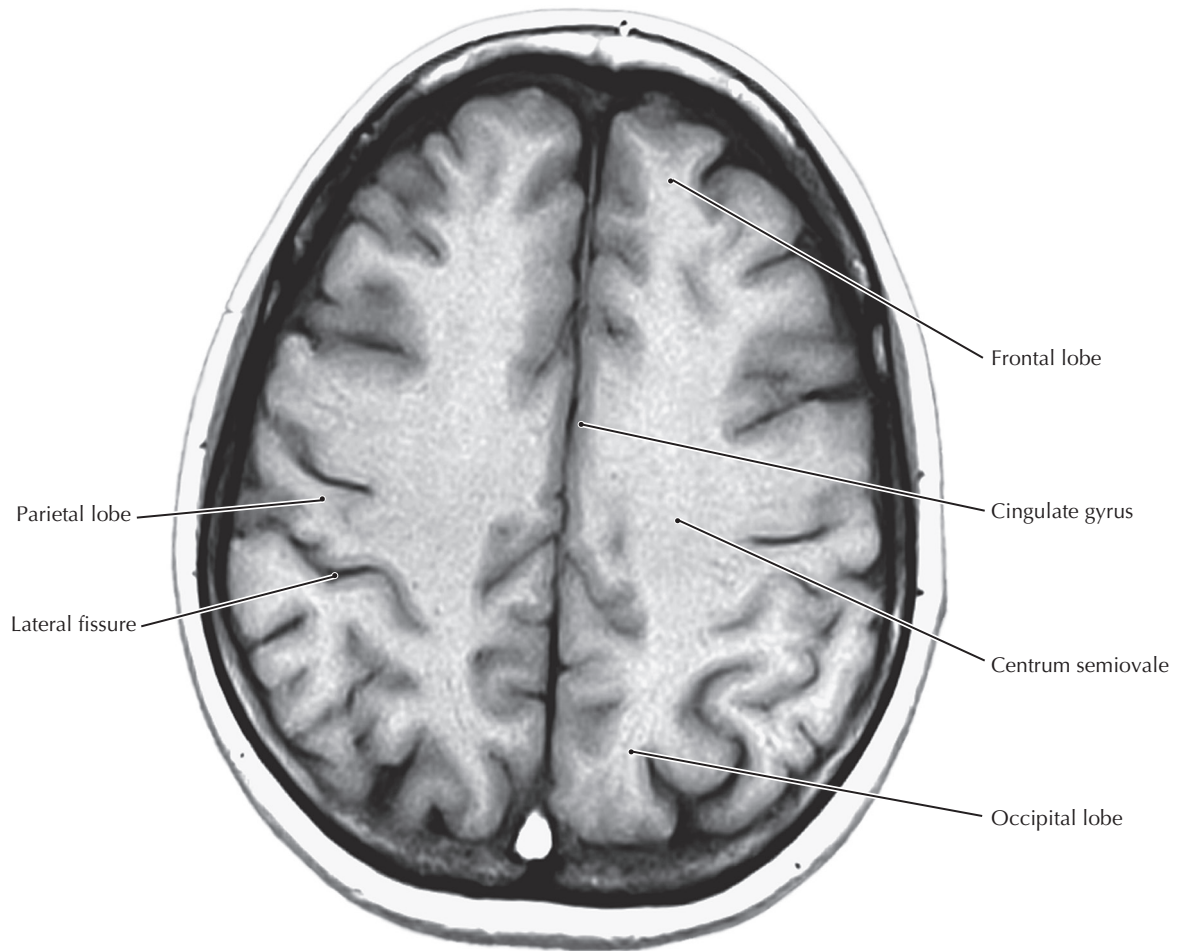
Level of section  
(centrum semiovale)



JOHN A. CRAIG MD

### 13.10A AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 10—CENTRUM SEMIOVALE

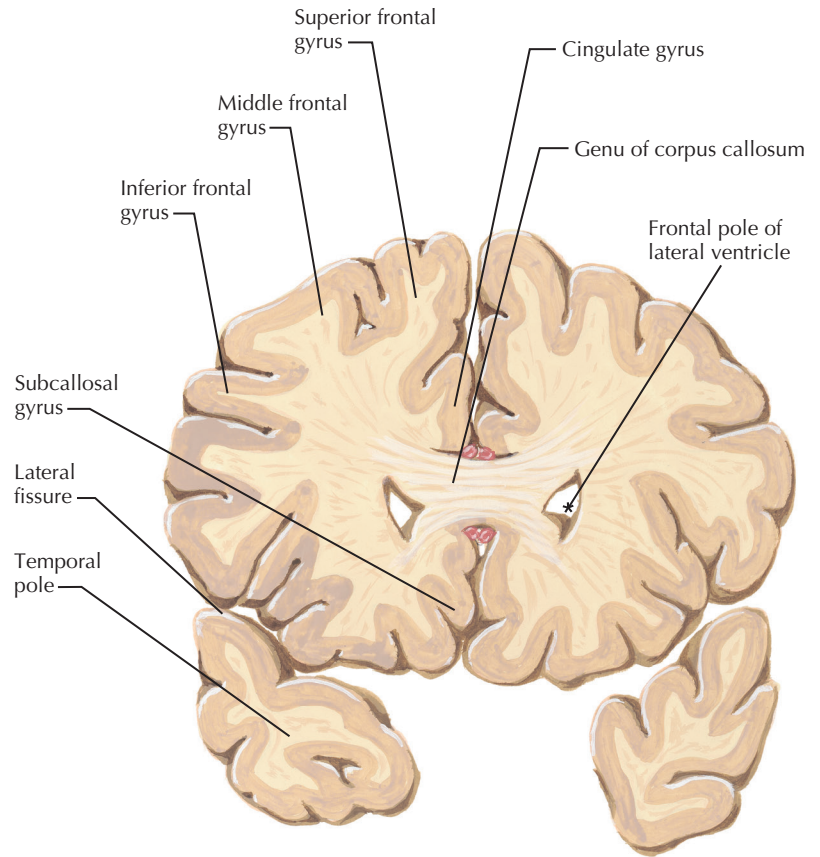
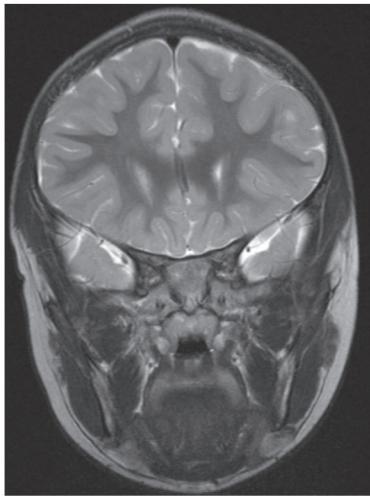
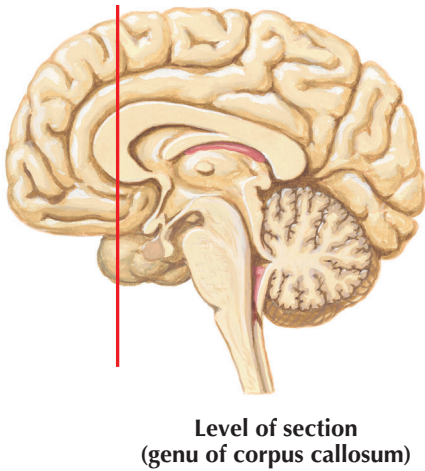
See [Video 13-1](#).



**13.10B AXIAL (HORIZONTAL) SECTIONS THROUGH THE FOREBRAIN: LEVEL 10—CENTRUM SEMIOVALE (CONTINUED)**



## Level 1: Genu of Corpus Callosum

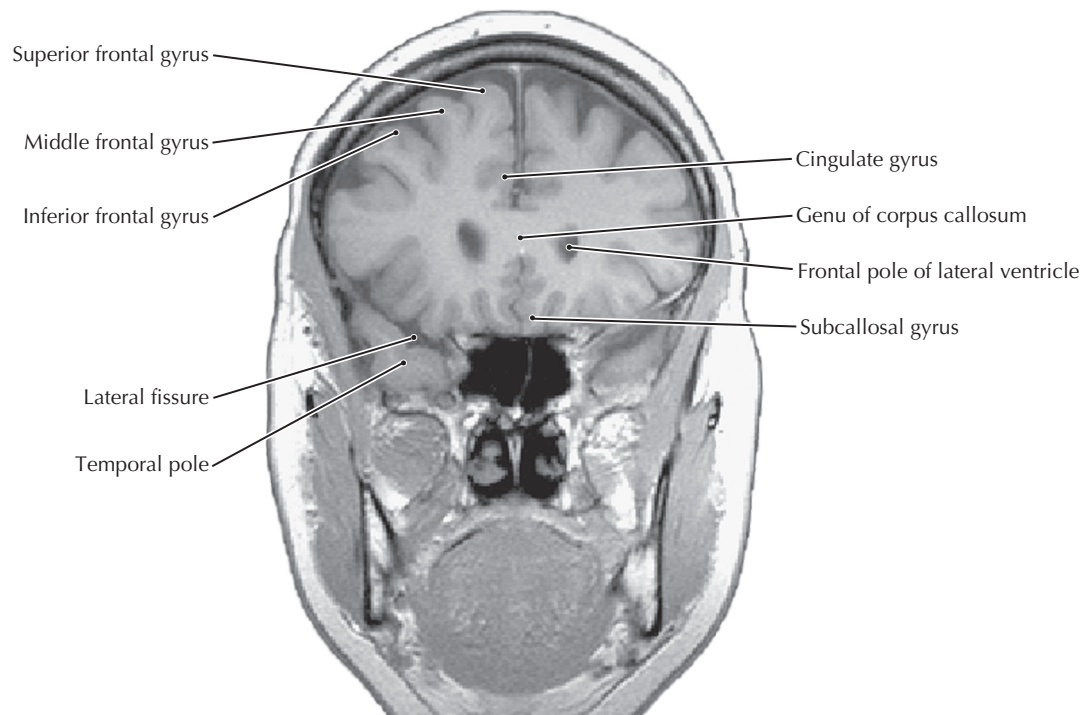


JOHN A. CRAIG, MD

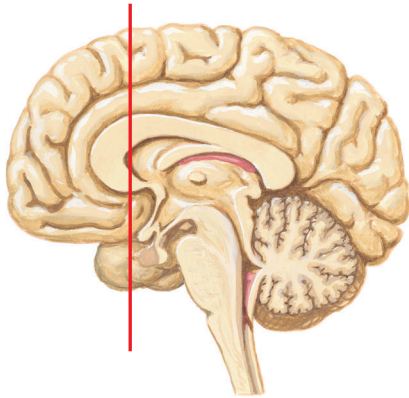
### 13.11A CORONAL SECTIONS THROUGH THE FOREBRAIN: LEVEL 1—GENU OF CORPUS CALLOSUM

These coronal sections compare anatomical sections and high-resolution MR images. They show important relationships among the internal capsule, basal ganglia, and thalamus. These sections show basal forebrain structures, such as nucleus accumbens, substantia innominata, and nucleus basalis (cho-

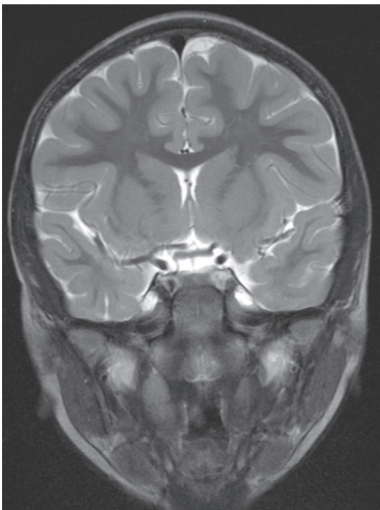
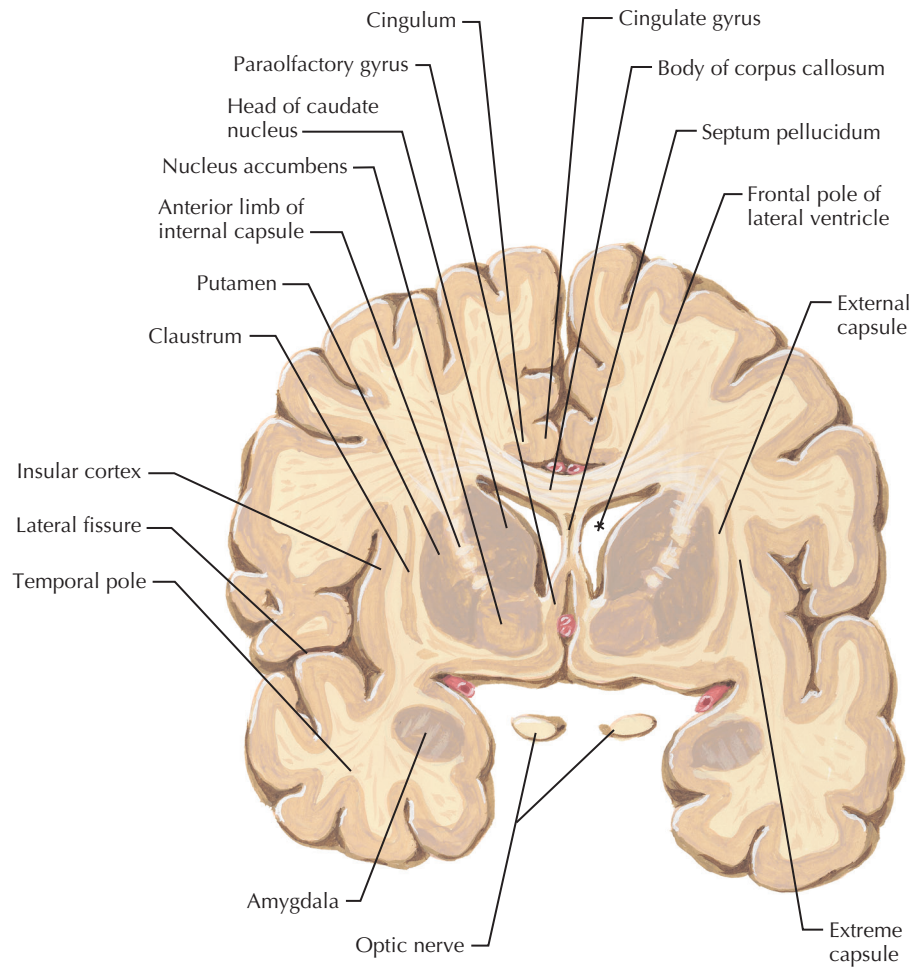
linergic forebrain nucleus), some individual thalamic nuclei, and the important temporal lobe structures (amygdaloid nuclei, hippocampal formation) and pathways (fornix, stria terminalis). The full-page MR images are T1-weighted; the ventricles appear dark. The scout MR images that accompany the drawings are T2-weighted MR images in which the CSF appears



## Level 2: Head of Caudate Nucleus/Nucleus Accumbens



Level of section  
(head of caudate nucleus/  
nucleus accumbens)



JOHN A. CRAIG MD

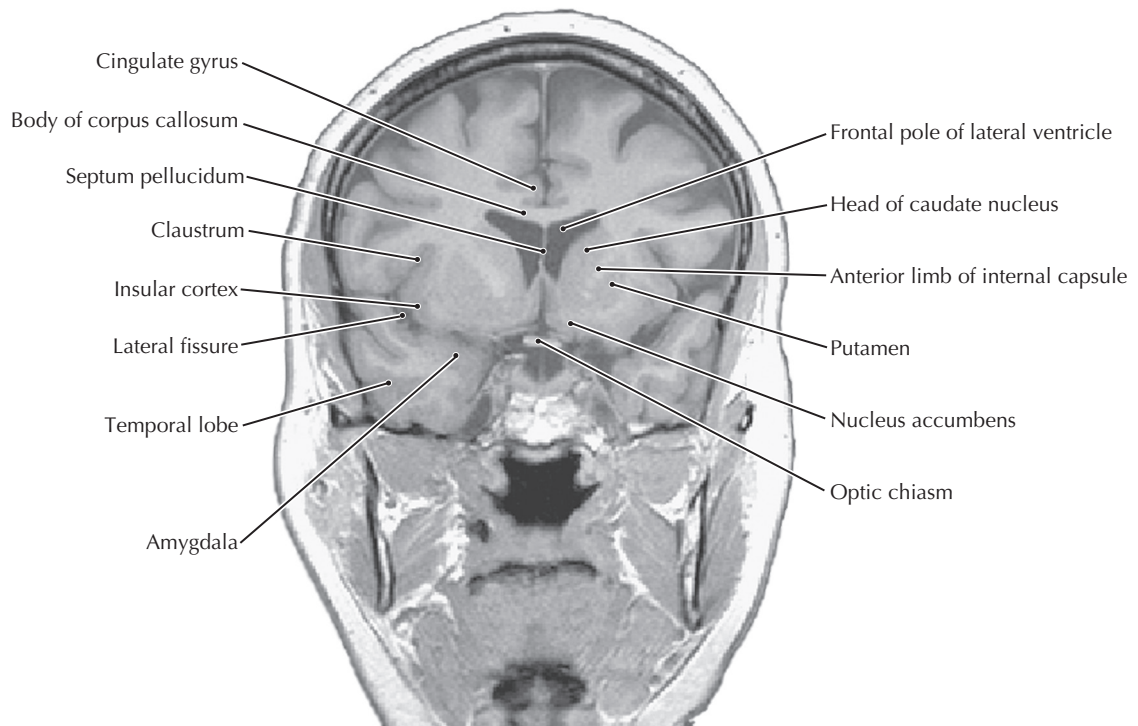
### 13.12A CORONAL SECTIONS THROUGH THE FOREBRAIN: LEVEL 2—HEAD OF CAUDATE NUCLEUS/NUCLEUS ACCUMBENS

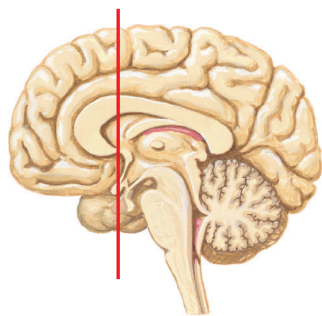
#### CLINICAL POINT

The nucleus accumbens is located at the anterior end of the striatum in the ventral part of the forebrain. It receives a variety of inputs from limbic structures, such as the amygdala, hippocampal formation, and

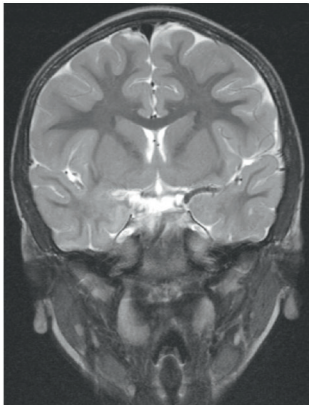
bed nucleus of the stria terminalis. A major dopaminergic (DA) input innervates the nucleus accumbens via the mesolimbic DA pathway, which derives from the ventral tegmental area in the ventral midbrain. The nucleus accumbens is central to motivational states and addictive behavior, driven by DA neurotransmission. The nucleus accumbens is also a principal region of brain circuitry associated with reward, such as joy, pleasure, and gratification. This nucleus has a looped circuitry through the thalamus and cortex that helps to provide motor expression of emotional responses and accompanying gestures and behaviors.



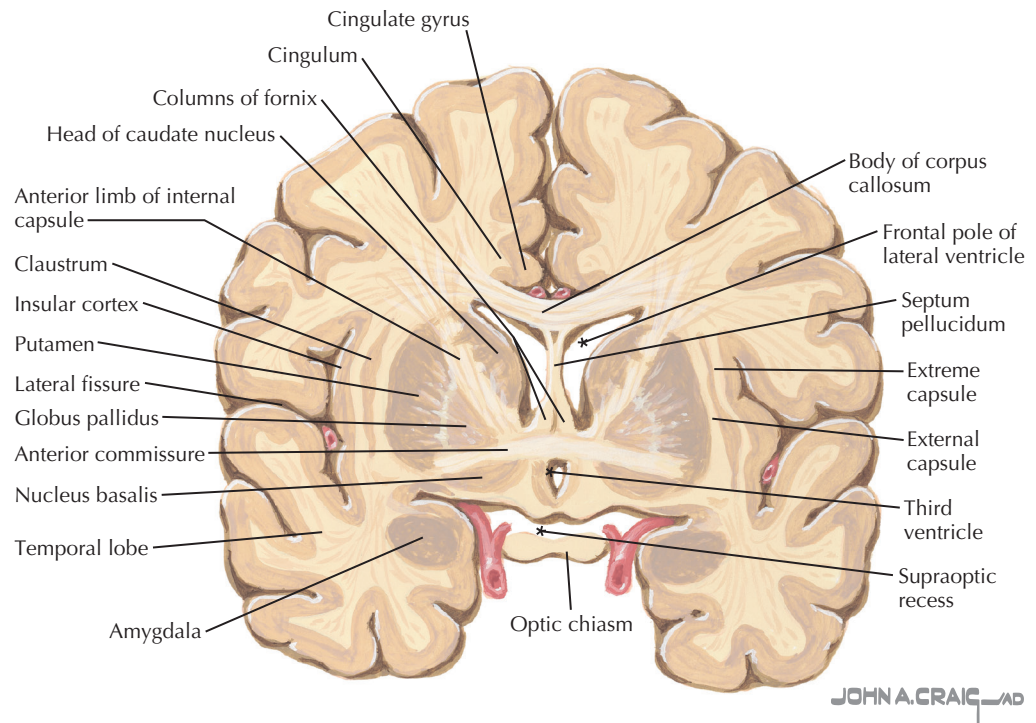




Level of section (anterior commissure/columns of fornix)



### Level 3: Anterior Commissure/Columns of Fornix



## 13.13A CORONAL SECTIONS THROUGH THE FOREBRAIN: LEVEL 3—ANTERIOR COMMISSURE/COLUMNS OF FORNIX

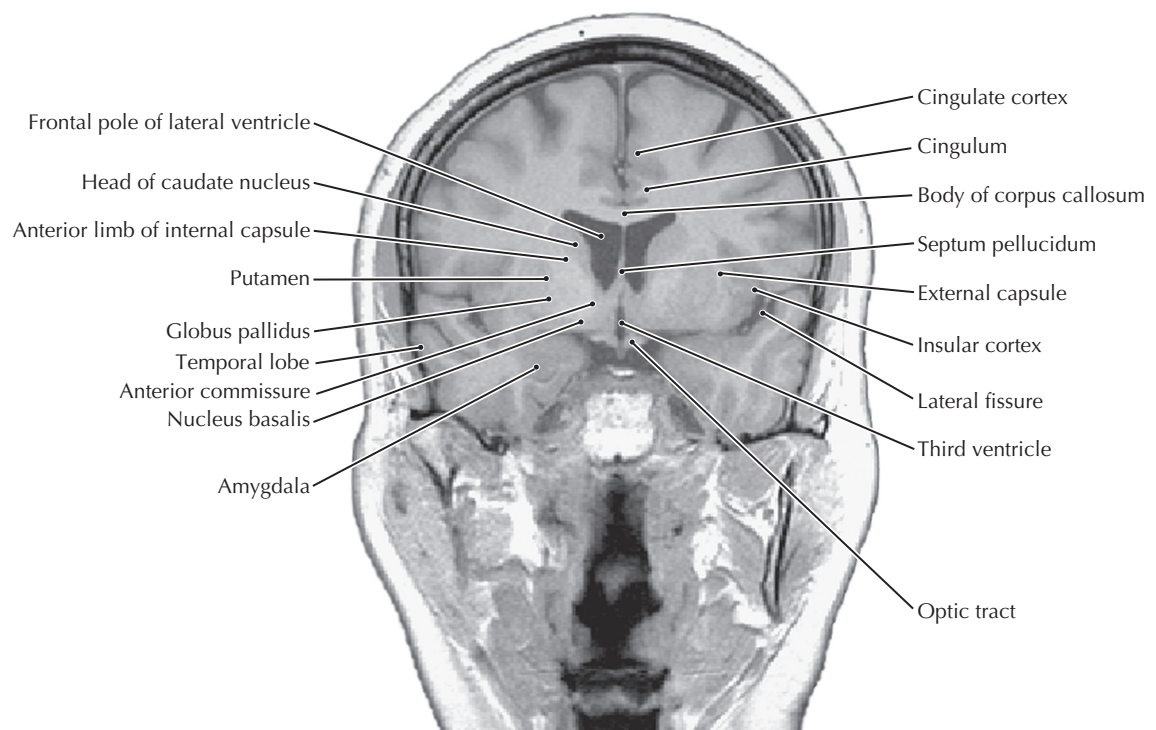
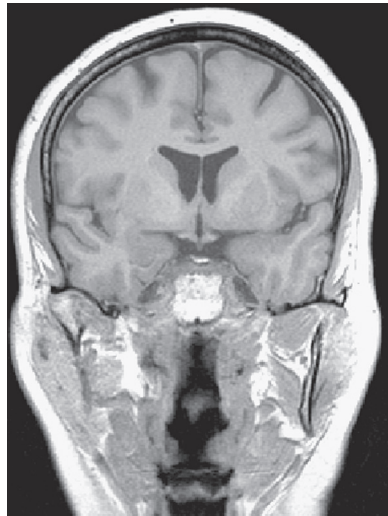
### CLINICAL POINT

Most infections in the brain are caused by viruses, bacteria, fungi, and other living organisms. A review of these infections is beyond the scope of this atlas. A prominent but rare exception to the norm is an unusual and unexpected *protein infection* (or *prion*) that is readily transmissible by a nonliving molecule, a protein. A normal neural protein, prion protein ( $\text{PrP}^c$ , c = cellular) functions as a copper-binding protein and is involved in cellular adhesion and cellular communication in neurons. An aberrant form of this protein ( $\text{PrP}^{Sc}$ , Sc = scrapie) displays an altered, aberrant folding structure. This aberrant protein form can recruit normal protein  $\text{PrP}^c$  to transform to the aberrant form,  $\text{PrP}^{Sc}$ , and form large, insoluble clusters of highly damaging amyloid-like plaques. The end result, after an incubation period, is a rapid, progressive chain reaction leading to vacuolization and degeneration/destruction of virtually all CNS regions. This is referred to as a spongiform encephalopathy, and the prion disease is also known as Creutzfeldt-Jakob disease (CJD).

The clinical symptoms of prion disease are myriad and include cognitive decline, emotional alterations, behavioral and personality changes, speech and language loss, motor and myoclonic changes, severe ataxia, swallowing problems, perceptual changes, seizures, and many others. No brain region is protected, and prominent structural damage can be found in the cerebral cortex, limbic structures, basal ganglia, thalamus, cerebellum, brain stem, and spinal cord.

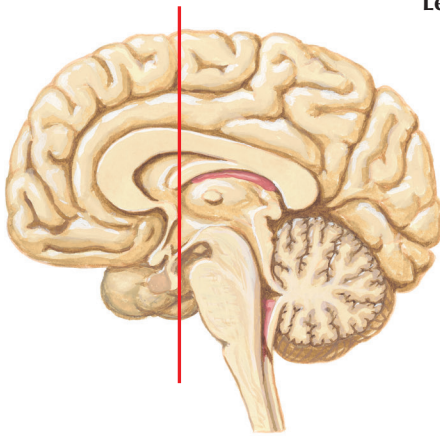
There are three major forms of prion disease. A genetic form (10% to 15% of cases) arises from an altered *PRNP* gene, which codes for the aberrant protein  $\text{PrP}^{Sc}$ . A spontaneous form, by far the largest number of cases, arises for unknown reasons (1 case per million individuals). A transmissible acquired form (variant CJD) arises from consumption of meat or body tissue from infected sheep and goats (scrapie), from cows (bovine spongiform encephalopathy) who were fed contaminated feed, leading to *bovine spongiform encephalopathy* in cows and *mad cow disease* in humans who eat the contaminated beef, and from wild game (deer, elk, with *chronic wasting disease*), and others. A rare acquired form was found many decades ago in Papua, New Guinea, in an indigenous tribe in which eating the brain tissue from other humans was practiced; this led to the disease *kuru*, which is also a prion disease.

These insoluble aberrant proteins also can be transmitted from individual to individual by medical procedures and the use of contaminated surgical instruments. It was found that even prolonged, vigorous autoclaving of surgical instruments or treatment with standard chemical disinfectants does not inactivate  $\text{PrP}^{Sc}$ . A special protocol is now required to ensure that prion disease can no longer be transmitted via this route. Ensurance of inactivation of the  $\text{PrP}^{Sc}$  protein occurs with incineration at  $1000^\circ\text{C}$ . There is no evidence for person to person transmission through normal human contact. At present, there is no known successful treatment for prion disease.

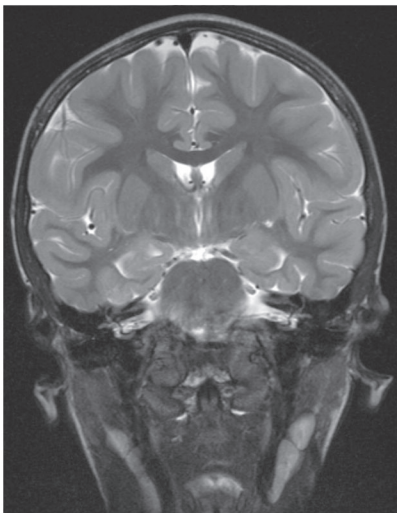
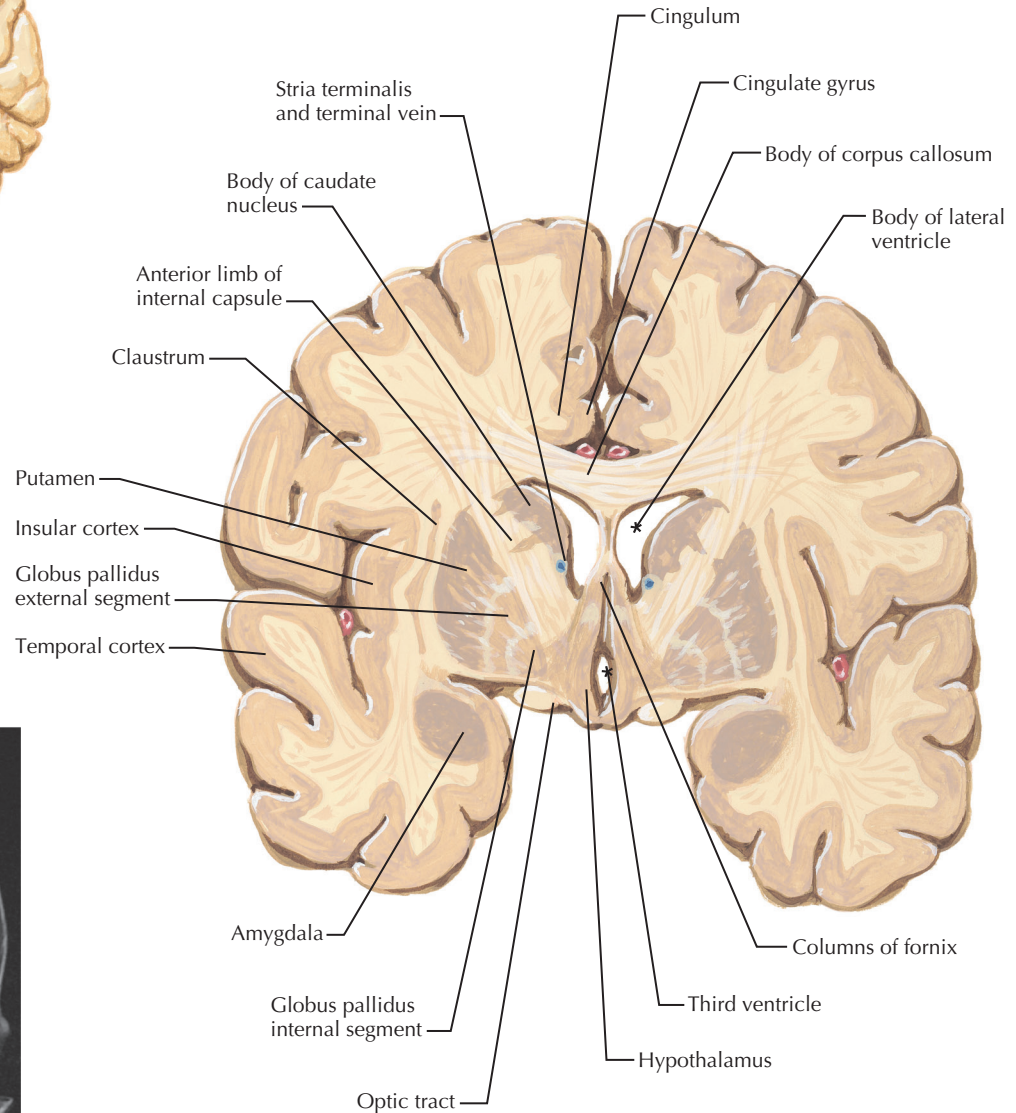




## Level 4: Amygdala, Anterior Limb of Internal Capsule



Level of section  
(amygdala, anterior limb  
of internal capsule)



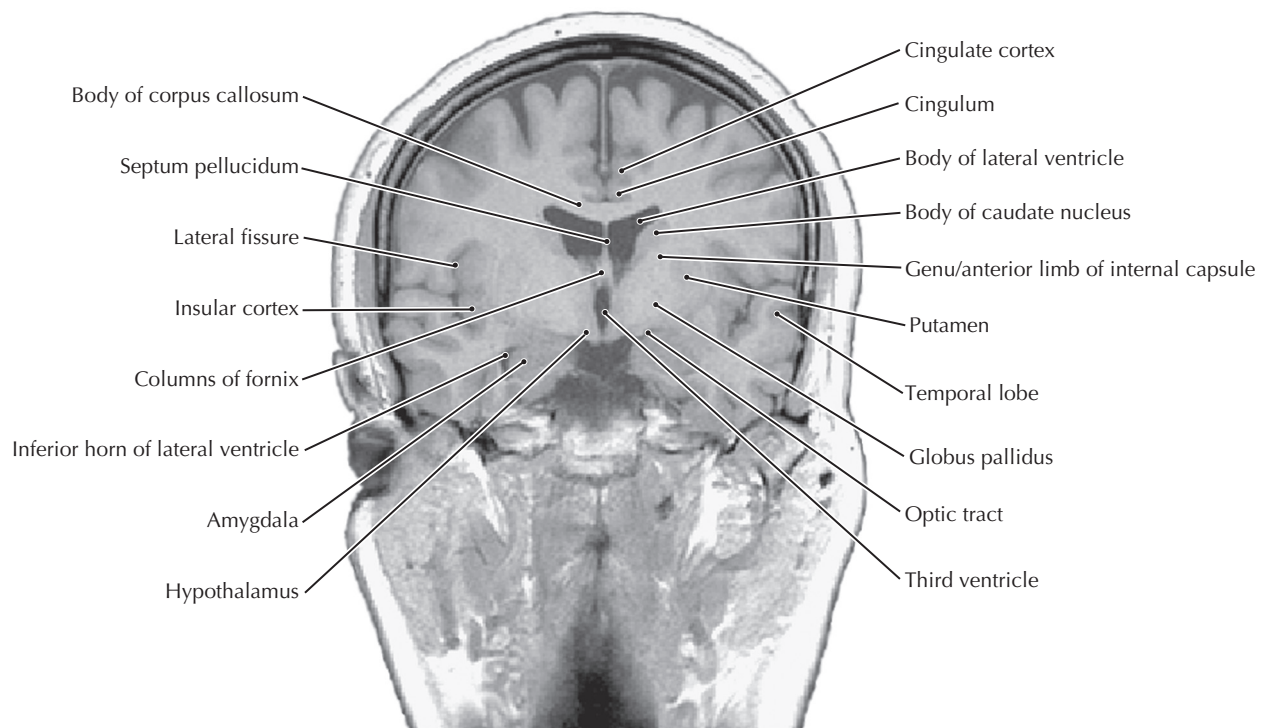
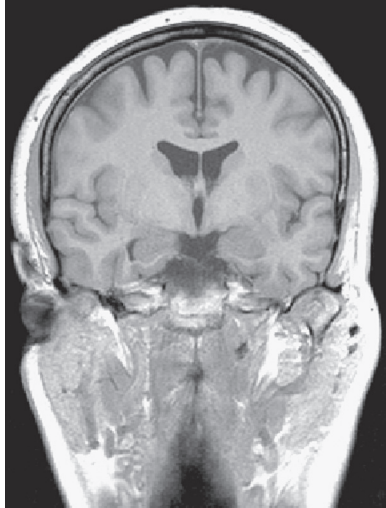
JOHN A. CRAIG MD

### 13.14A CORONAL SECTIONS THROUGH THE FOREBRAIN: LEVEL 4—AMYGDALA, ANTERIOR LIMB OF INTERNAL CAPSULE

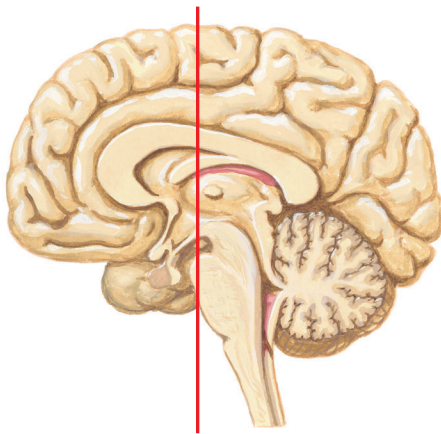
#### CLINICAL POINT

The corpus callosum is the principal interhemispheric or commissural pathway in the brain. It interconnects one hemisphere with its counterpart on the other side, with the exception of part of the temporal lobe that is interconnected by the anterior commissure. Some large lesions resulting from trauma or tumor can damage the corpus callosum, but this is usually accompanied by a large amount of additional

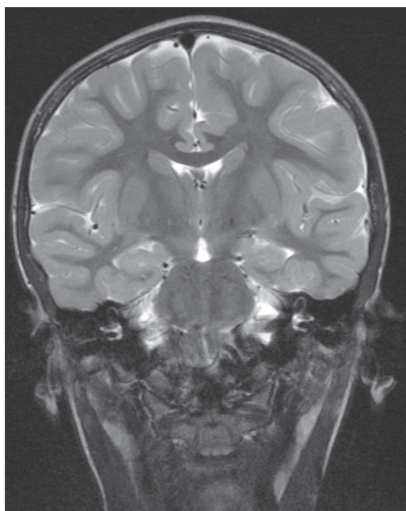
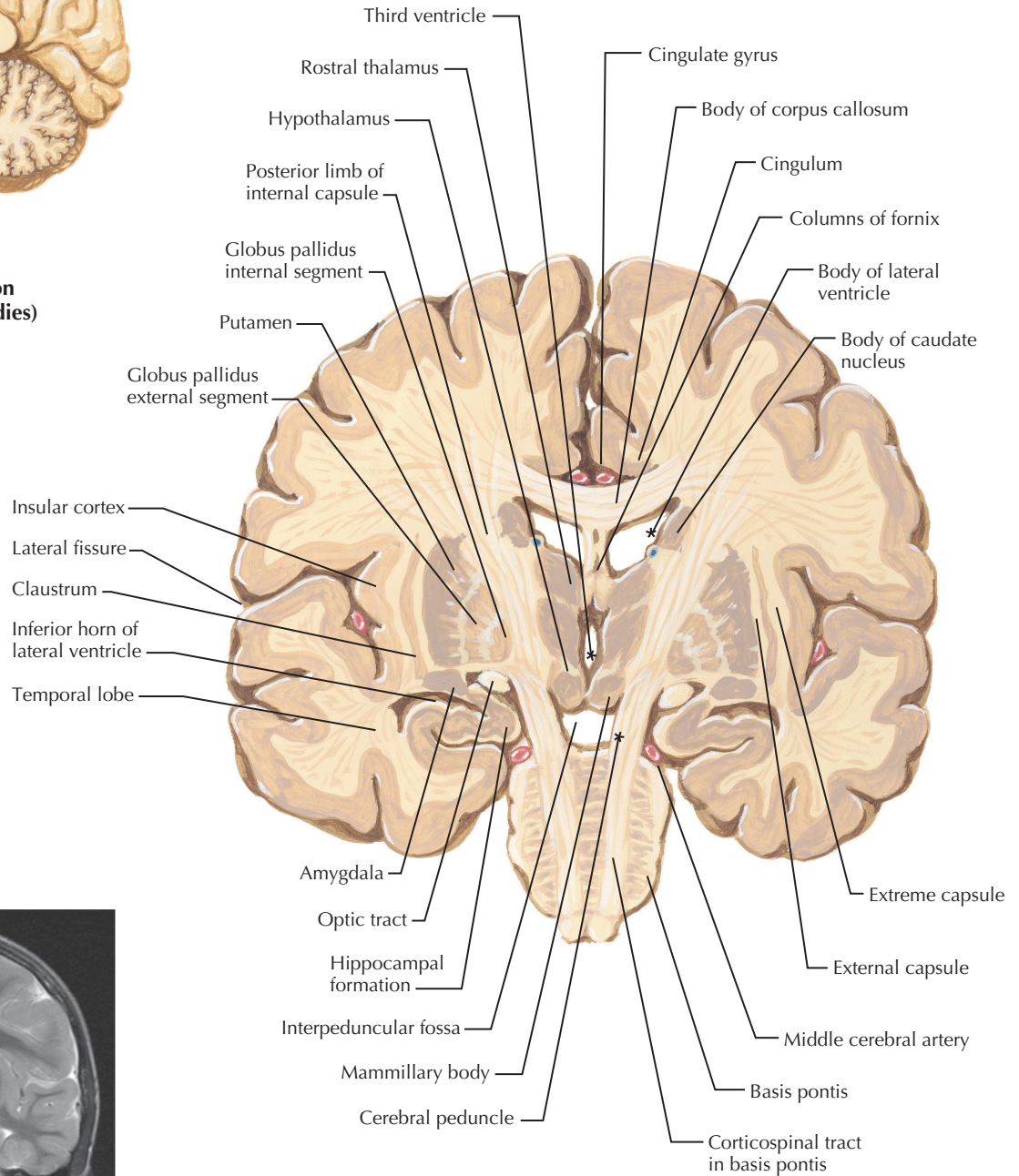
forebrain damage. However, specific surgical sectioning of the corpus callosum has been performed in an attempt to alleviate the spread of seizure activity from one side of the brain to the other. This “split-brain” surgery causes each hemisphere to be unaware of specific activity occurring in the other hemisphere. Thus, the left brain cannot identify a visual or somatosensory stimulus presented to the right hemisphere and does not know where the left hand and arm are located if they are kept from the left hemisphere’s view. Sometimes, the left hand may act independently of the conscious intent of the left hemisphere. Some emotional information appears to transfer through brain stem regions between the two parts of the split brain, providing a limbic context that may be perceived to some extent by both hemispheres.



### Level 5: Mammillary Bodies

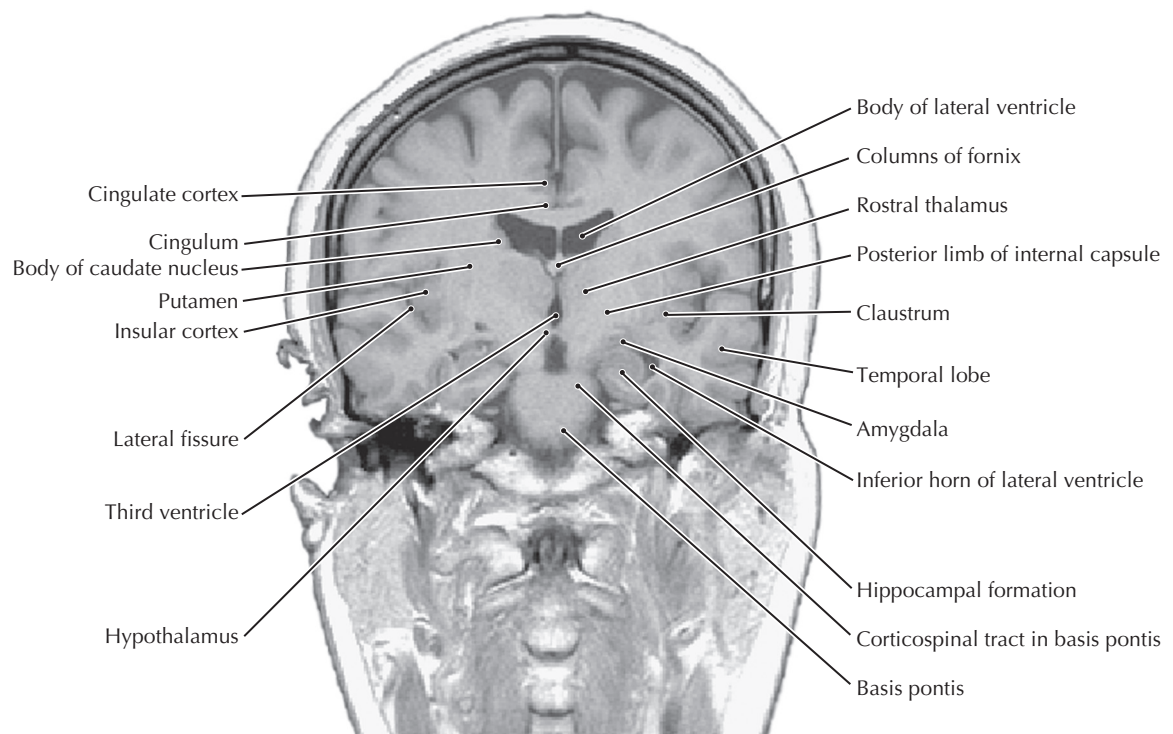
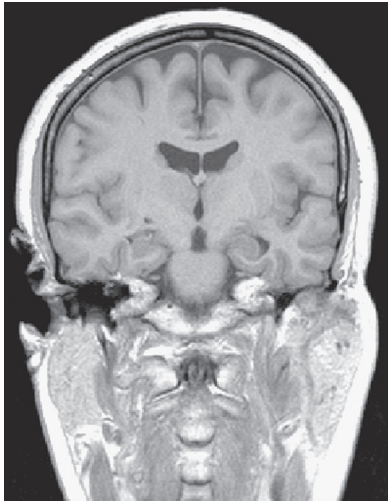


Level of section  
(mammillary bodies)

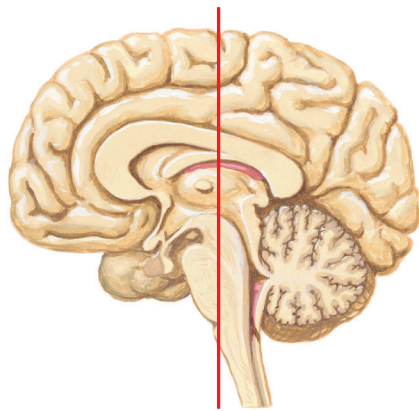


JOHN A. CRAIG, MD

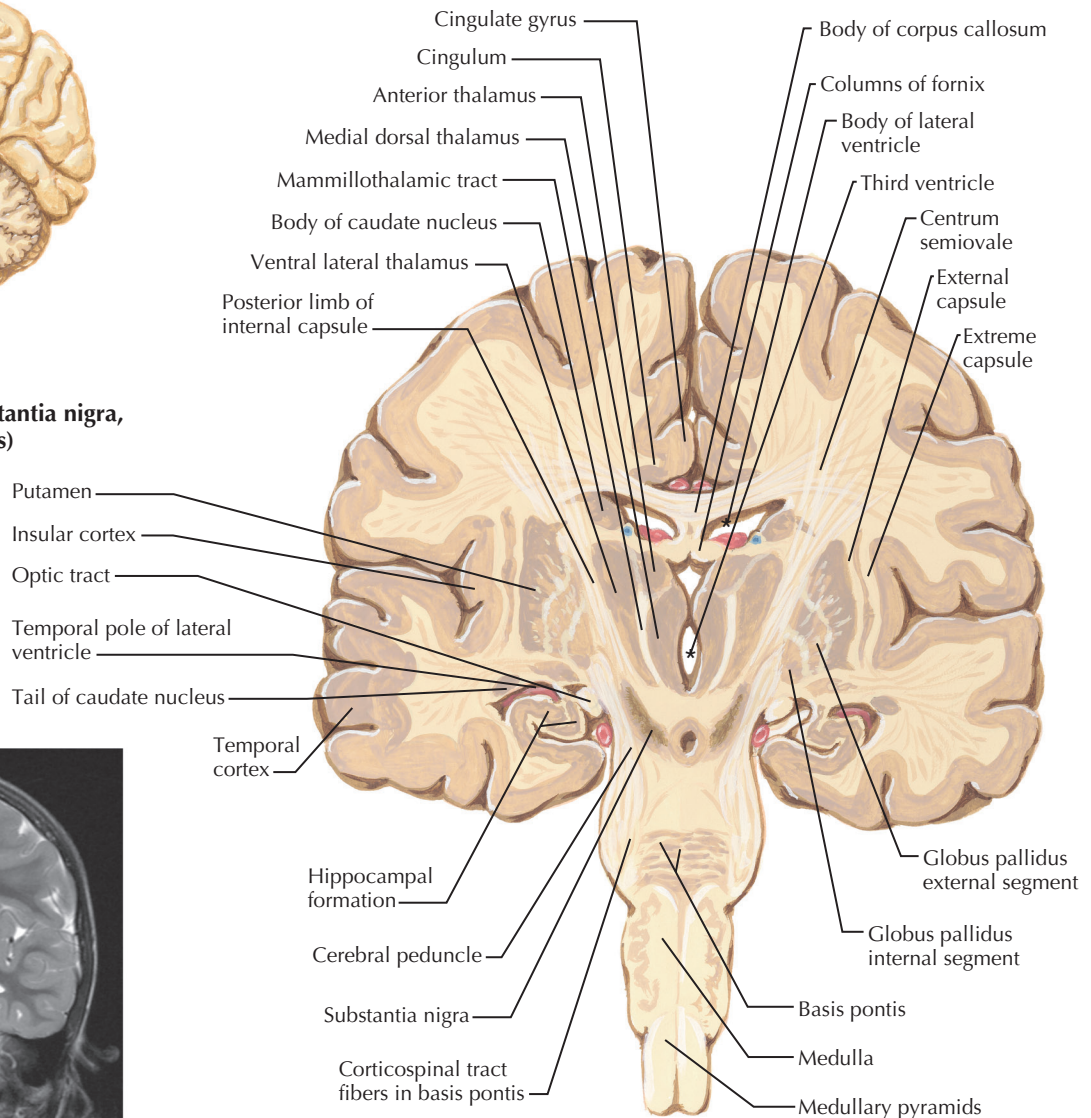
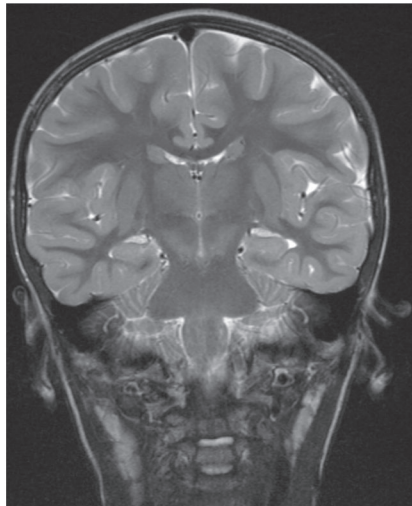




## Level 6: Mammillothalamic Tract/Substantia Nigra, Rostral Hippocampus



**Level of section**  
(mammillothalamic tract/substantia nigra,  
rostral hippocampus)



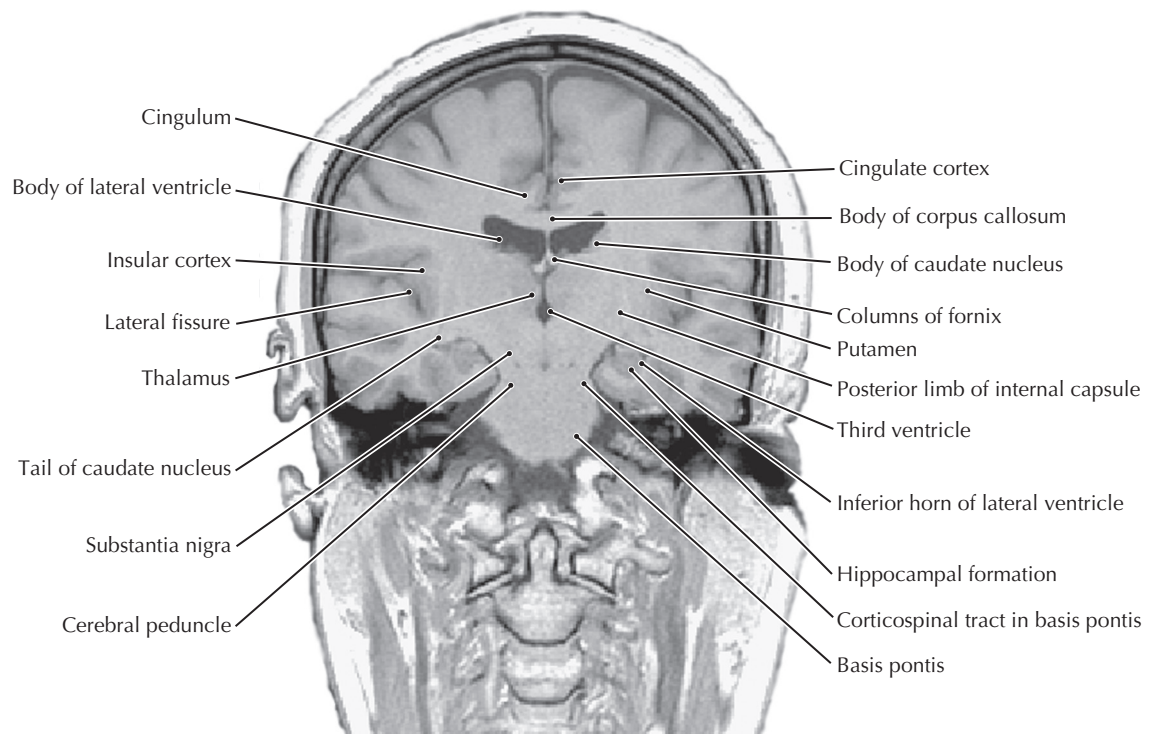
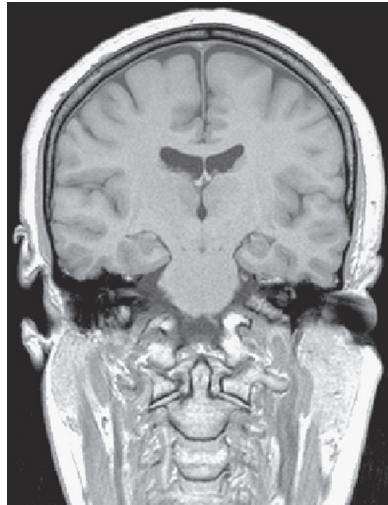
JOHN A. CRAIG MD

### 13.16A CORONAL SECTIONS THROUGH THE FOREBRAIN: LEVEL 6—MAMMILLOTHALAMIC TRACT/SUBSTANTIA NIGRA, ROSTRAL HIPPOCAMPUS

#### CLINICAL POINT

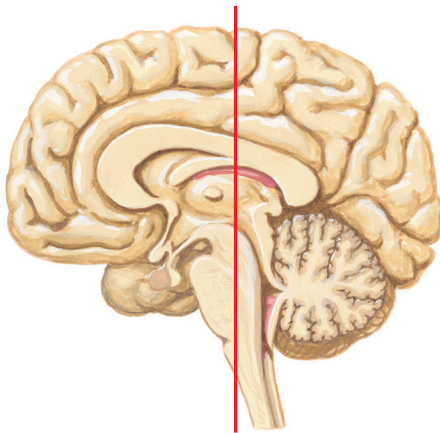
The posterior limb of the IC is the major afferent and efferent route through which the cerebral cortex is connected with the rest of the brain. The cerebral cortex sends descending fibers through the IC that are destined for the spinal cord, brain stem, cerebellum (via pontine nuclei), striatum and related nuclei, thalamus, and limbic structures. Of particular importance for movement are the corticospinal system and cortical connections to other upper motor neuron regions (such

as the red nucleus) arising from the motor and premotor/supplemental motor cortices, which help to control skilled movements of the contralateral limbs; and the corticobulbar tract, which supplies motor cranial nerve nuclei with descending control, all bilaterally except for the lower facial nucleus, which receives exclusively contralateral input. The corticospinal tract travels in the posterior limb of the IC, and the corticobulbar tract travels in the genu of the IC. The posterior limb of the IC also conveys the ascending somatosensory and trigeminal sensory axons from the ventral posterolateral and posteromedial thalamus, which are susceptible to vascular infarcts in the middle cerebral artery and fine penetrating lenticulostriate arteries. Such an infarct acutely produces contralateral hemiplegia and a drooping lower face, with loss of somatic sensation. With time, the hemiplegia becomes spastic, with hyperreflexia, hypertonus, and pathological reflexes (Babinski's reflex, or plantar extensor response).

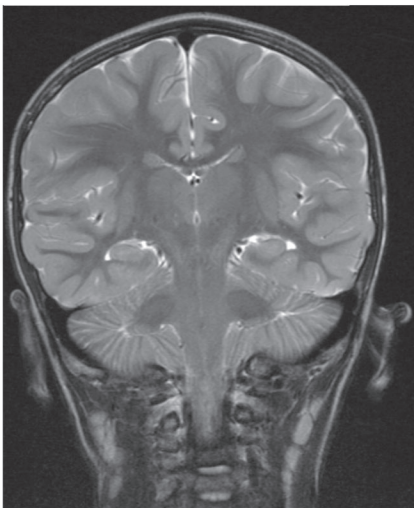
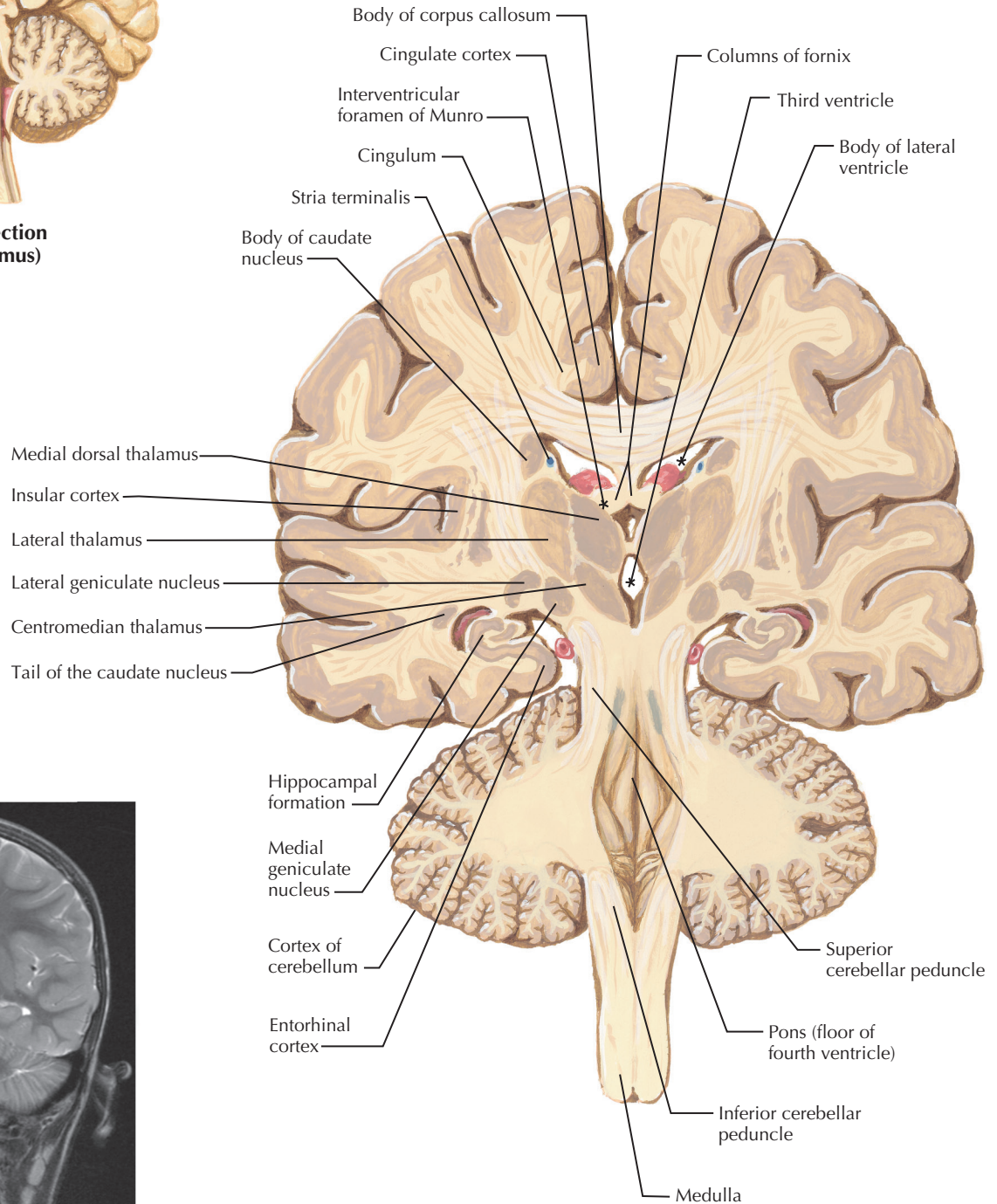




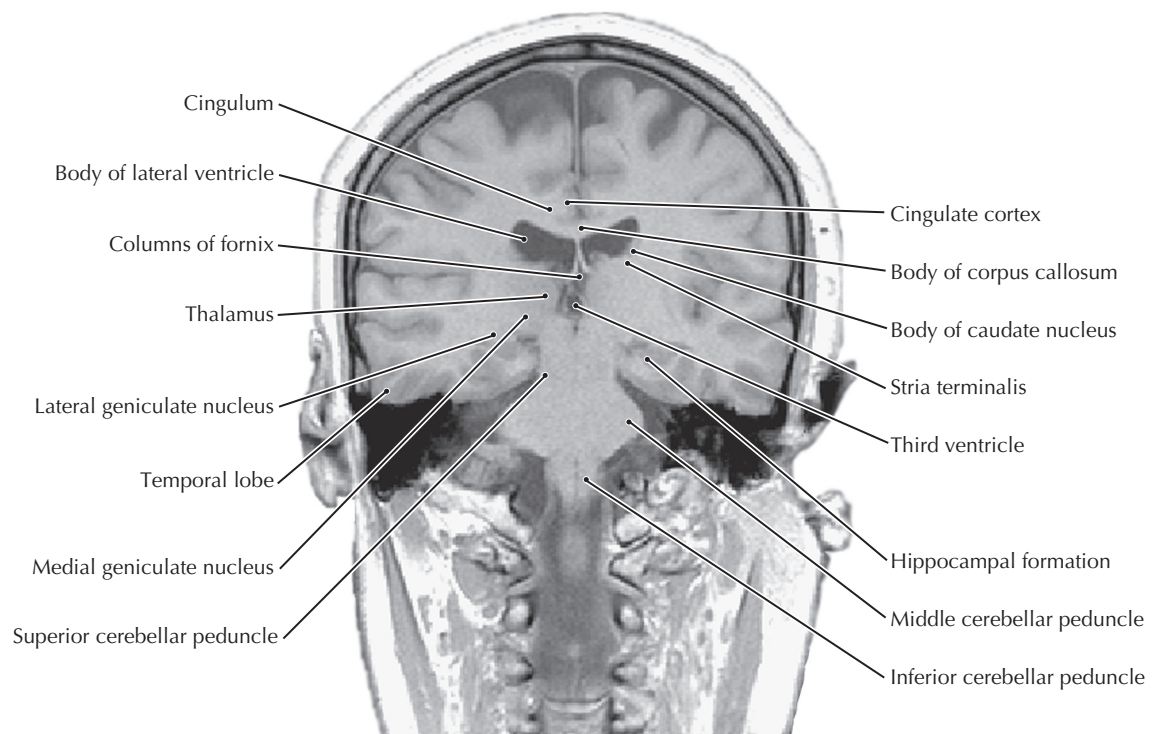
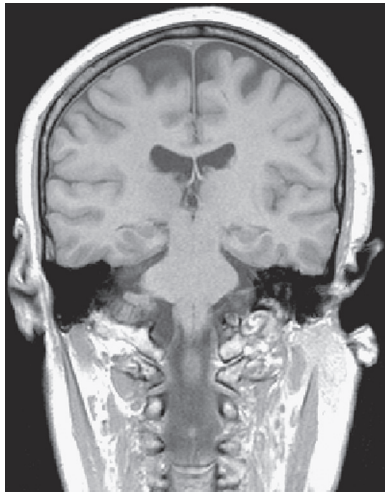
Level 7: Midthalamus



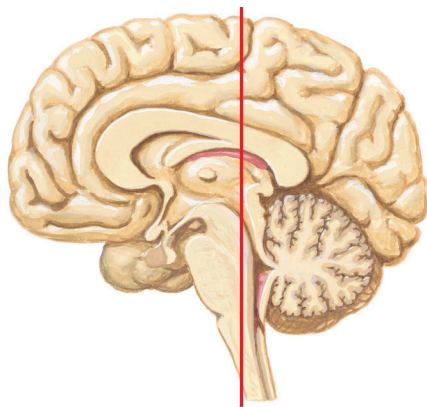
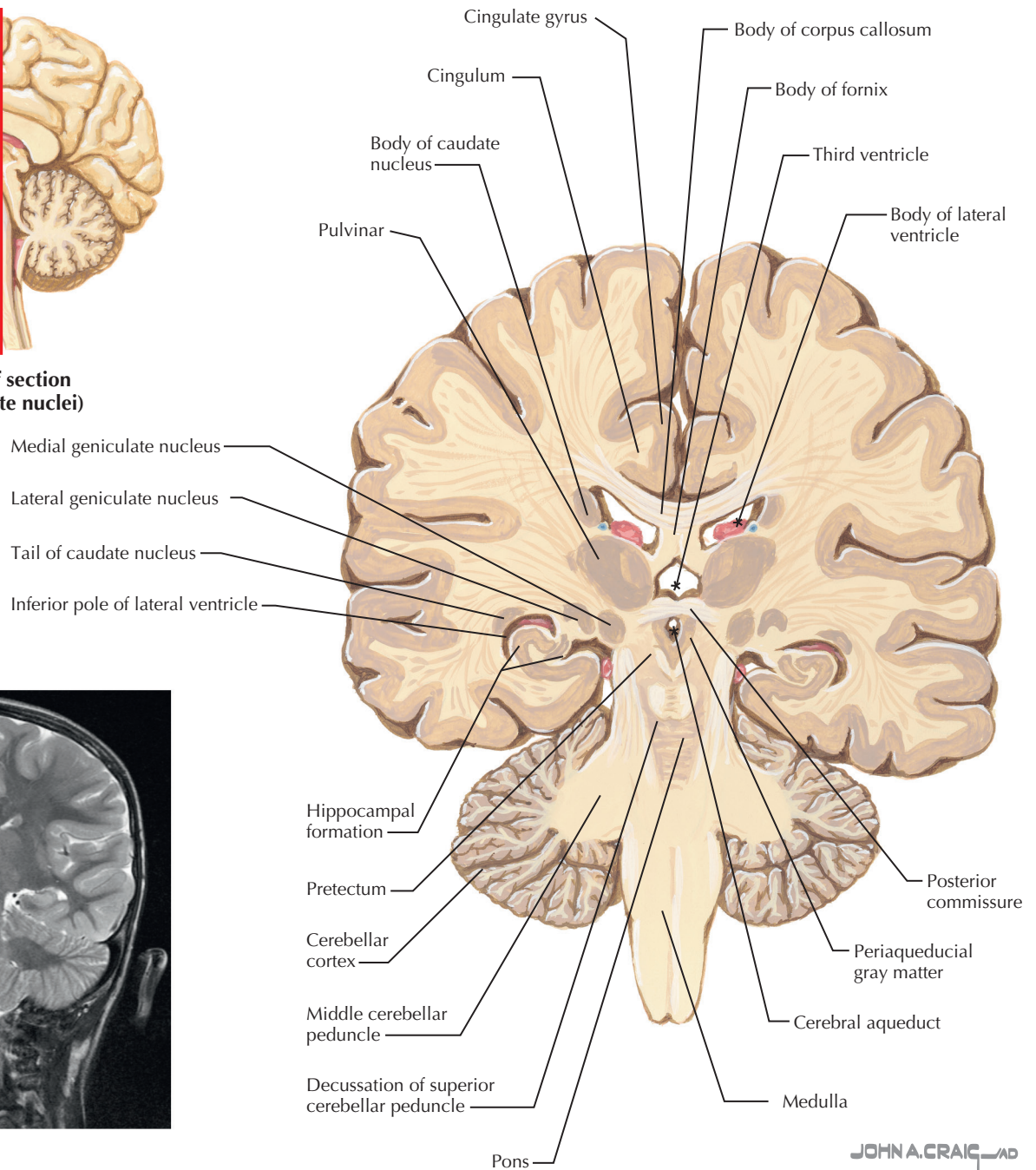
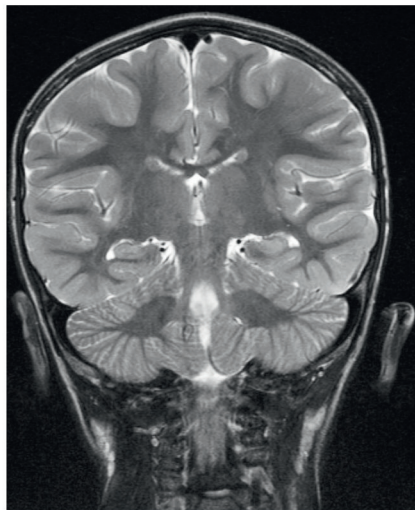
Level of section  
(midthalamus)



JOHN A. CRAIG, MD



## Level 8: Geniculate Nuclei

Level of section  
(geniculate nuclei)

JOHN A. CRAIG

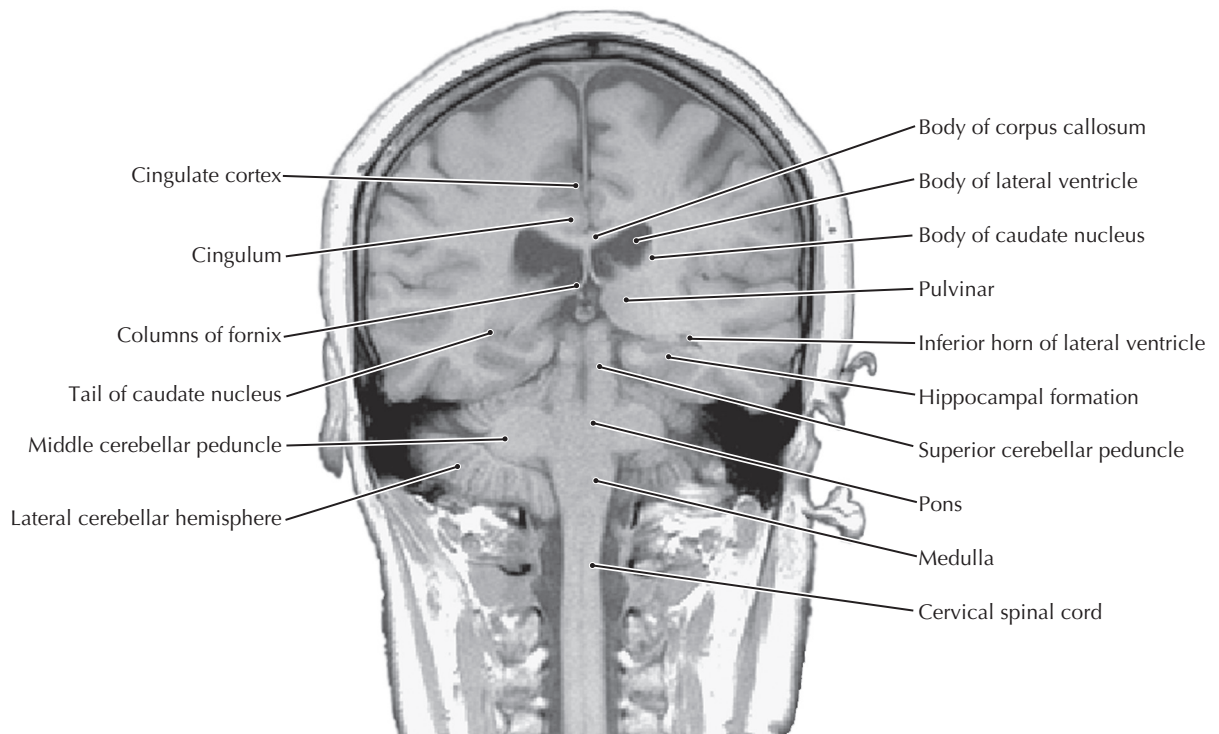
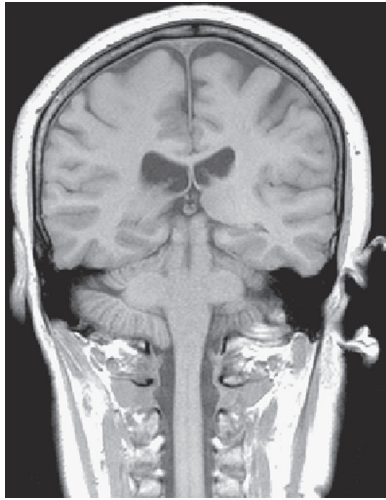
## 13.18A CORONAL SECTIONS THROUGH THE FOREBRAIN: LEVEL 8—GENICULATE NUCLEI

## CLINICAL POINT

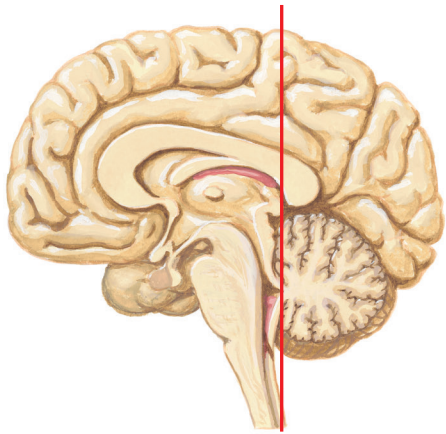
Several thalamic nuclei in the posterior thalamus are important for conveying visual and auditory information to the cerebral cortex. The lateral geniculate nucleus receives segregated input from the temporal hemiretina of the ipsilateral eye and from the nasal hemiretina of the contralateral eye, and it conveys this topographical information to area 17, the primary visual cortex, located on the banks of the calca-

rine fissure. A lesion in the lateral geniculate nucleus results in contralateral hemianopia. The pulvinar receives visual input from the superior colliculus and also conveys visual information to the visual cortex, to areas 18 and 19 (associative visual cortex). A lesion in the pulvinar can lead to contralateral visual neglect. The medial geniculate nucleus receives input from the inferior colliculus through the brachium of the inferior colliculus. However, because the auditory system is bilaterally represented at this level, a lesion in the medial geniculate nucleus on one side does not result in contralateral deafness. There may be some diminution of hearing contralateral to the lesion, but it is not a profound deficit. Visual areas 17, 18, and 19 correspond to visual cortices I, II, and III, as illustrated in [Figure 13.26](#).

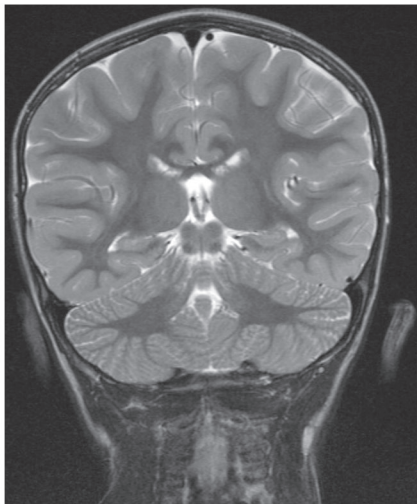
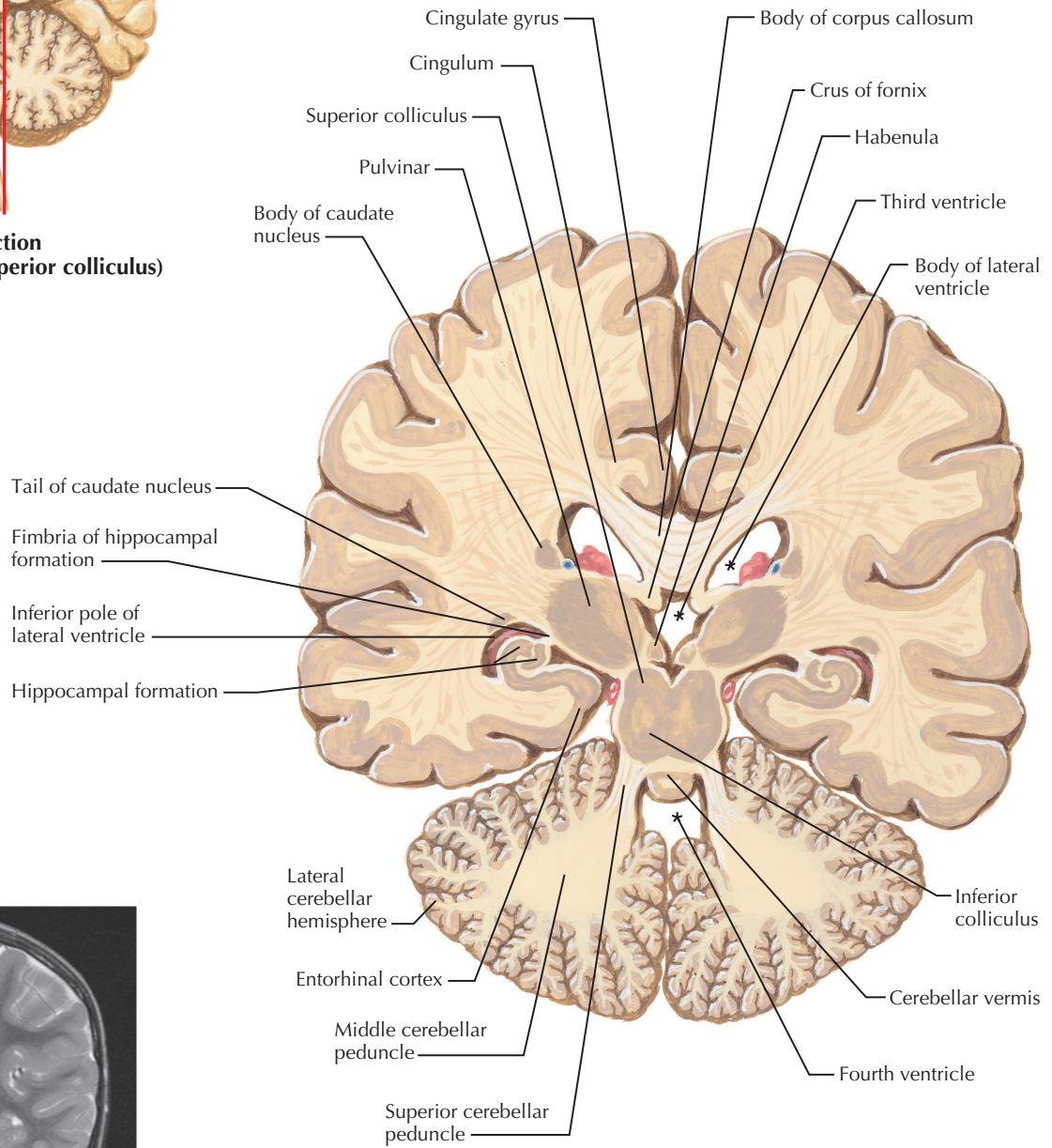




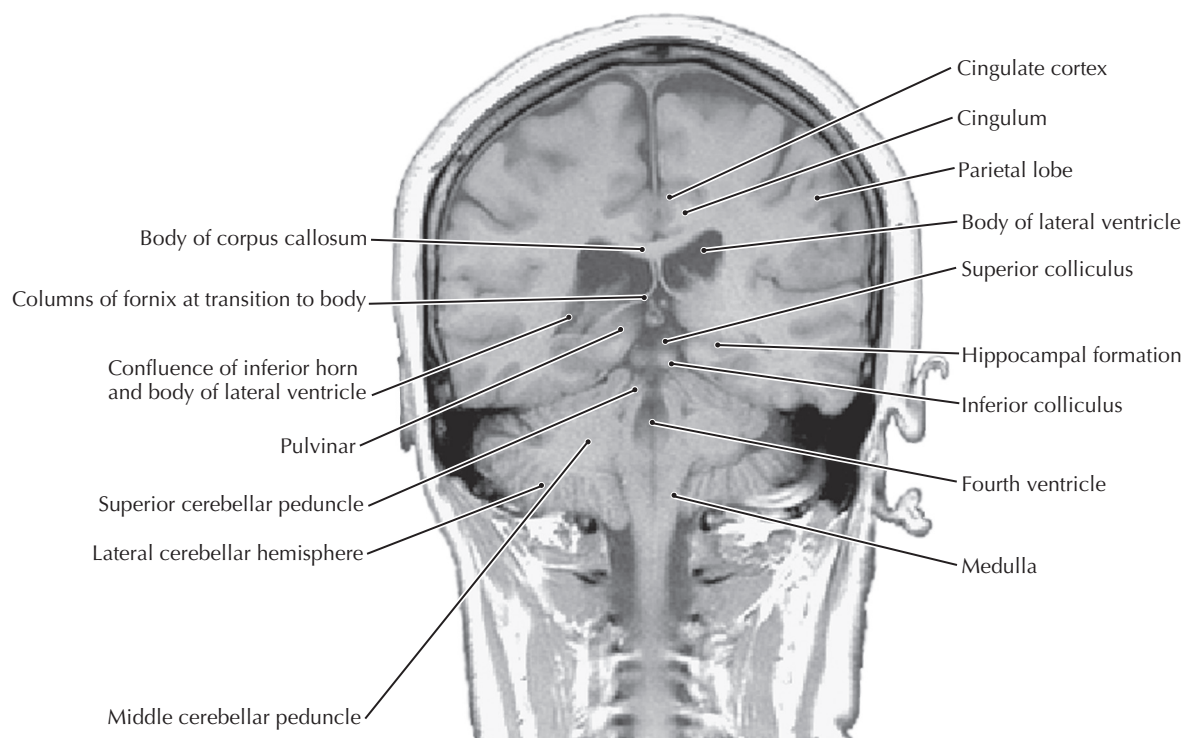
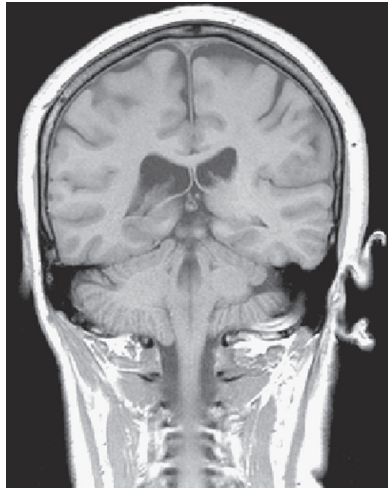
Level 9: Caudal Pulvinar and Superior Colliculus



Level of section  
(caudal pulvinar and superior colliculus)

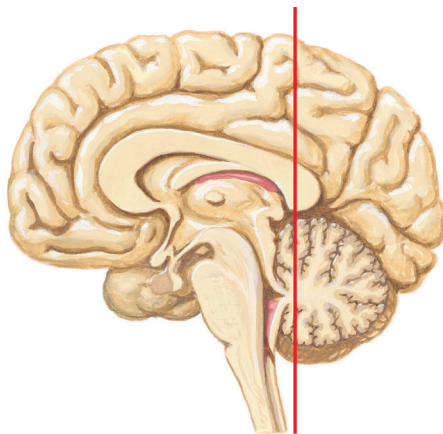


JOHN A. CRAIG MD

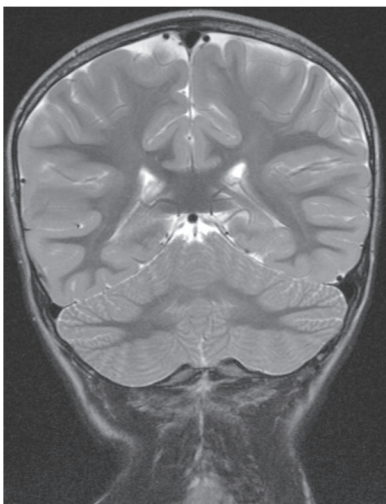
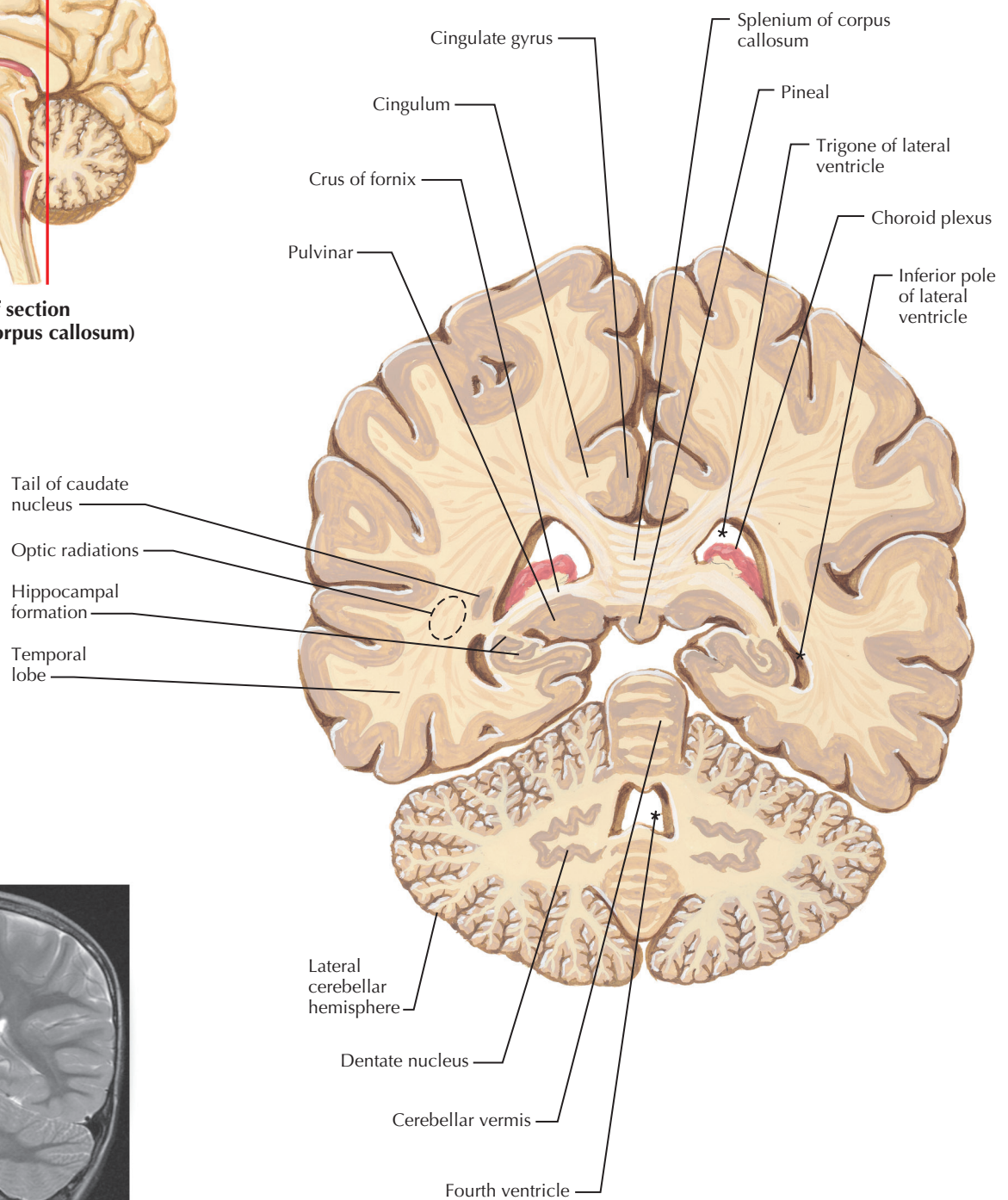




# Level 10: Splenium of Corpus Callosum



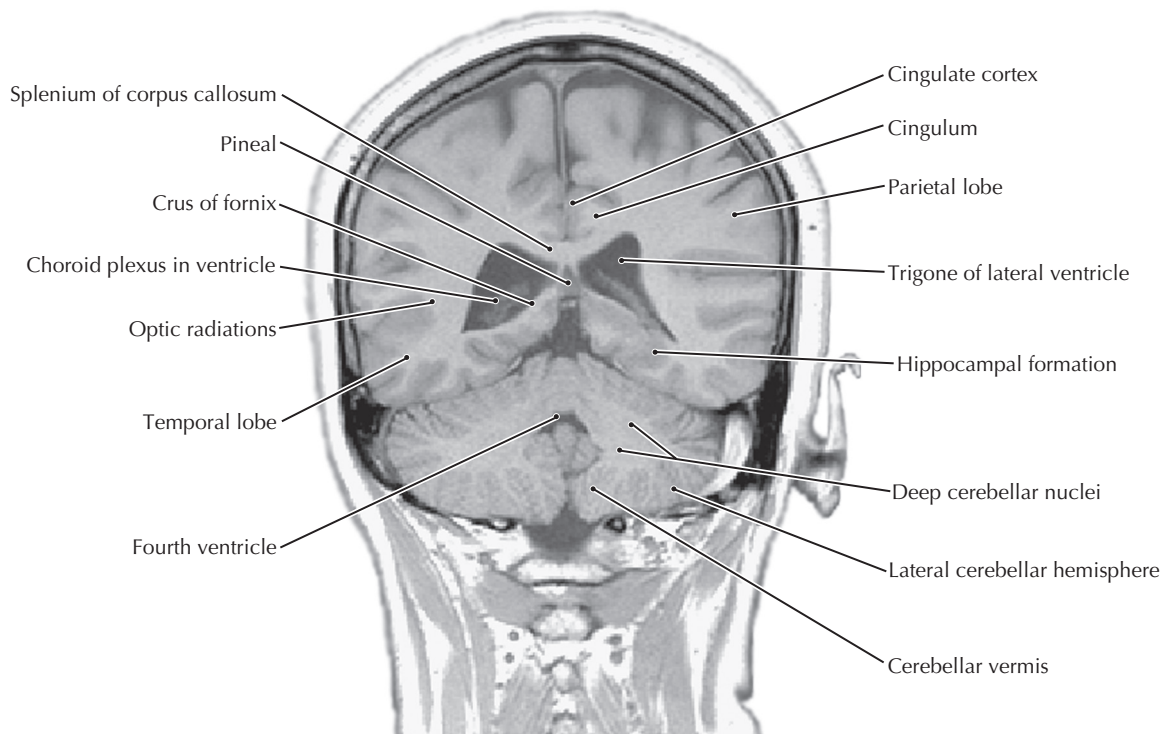
Level of section  
(splenium of corpus callosum)

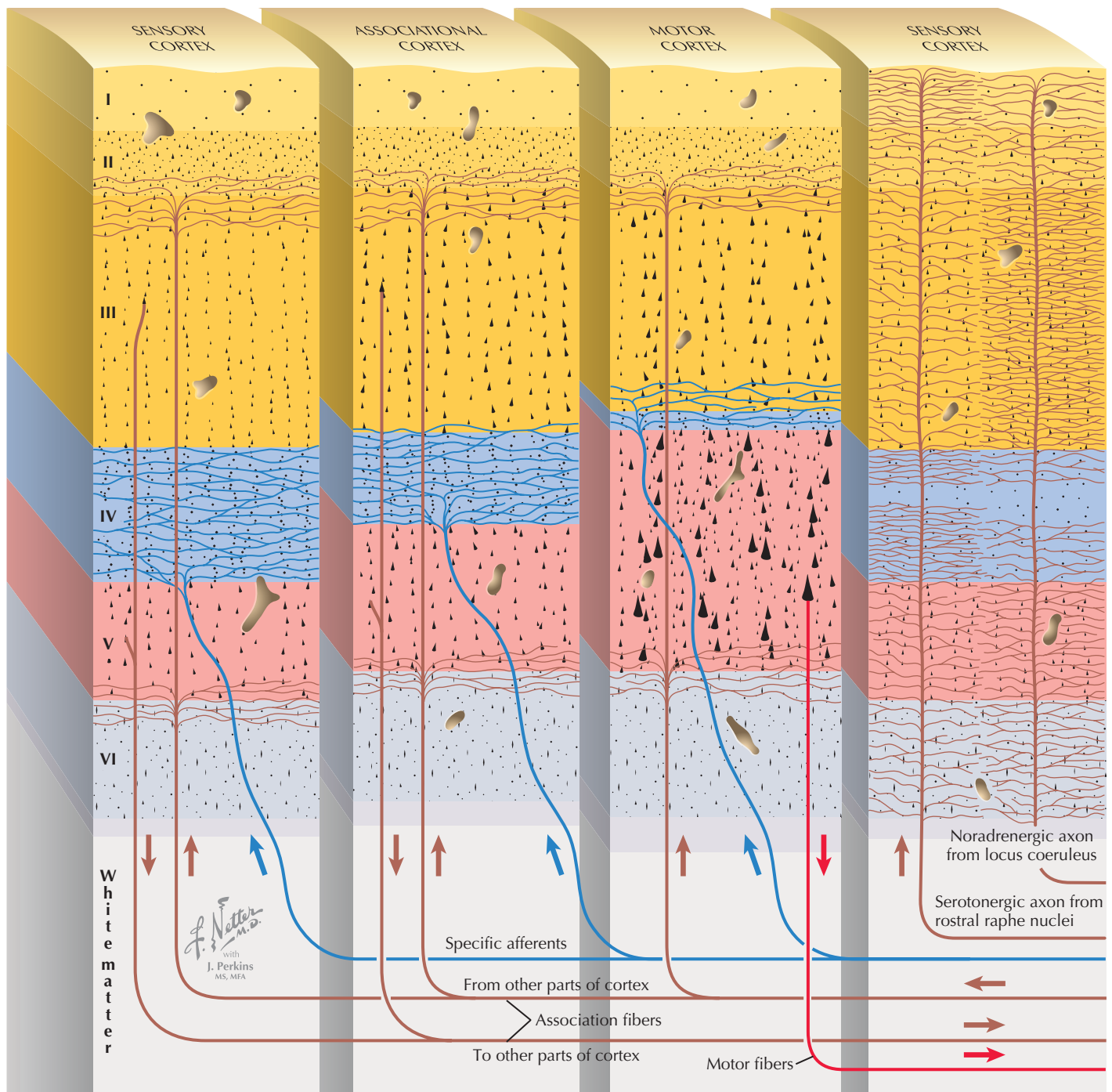


JOHN A. CRAIG AD

## 13.20A CORONAL SECTIONS THROUGH THE FOREBRAIN: LEVEL 10—SPLENIUM OF CORPUS CALLOSUM

See [Video 13-2](#).



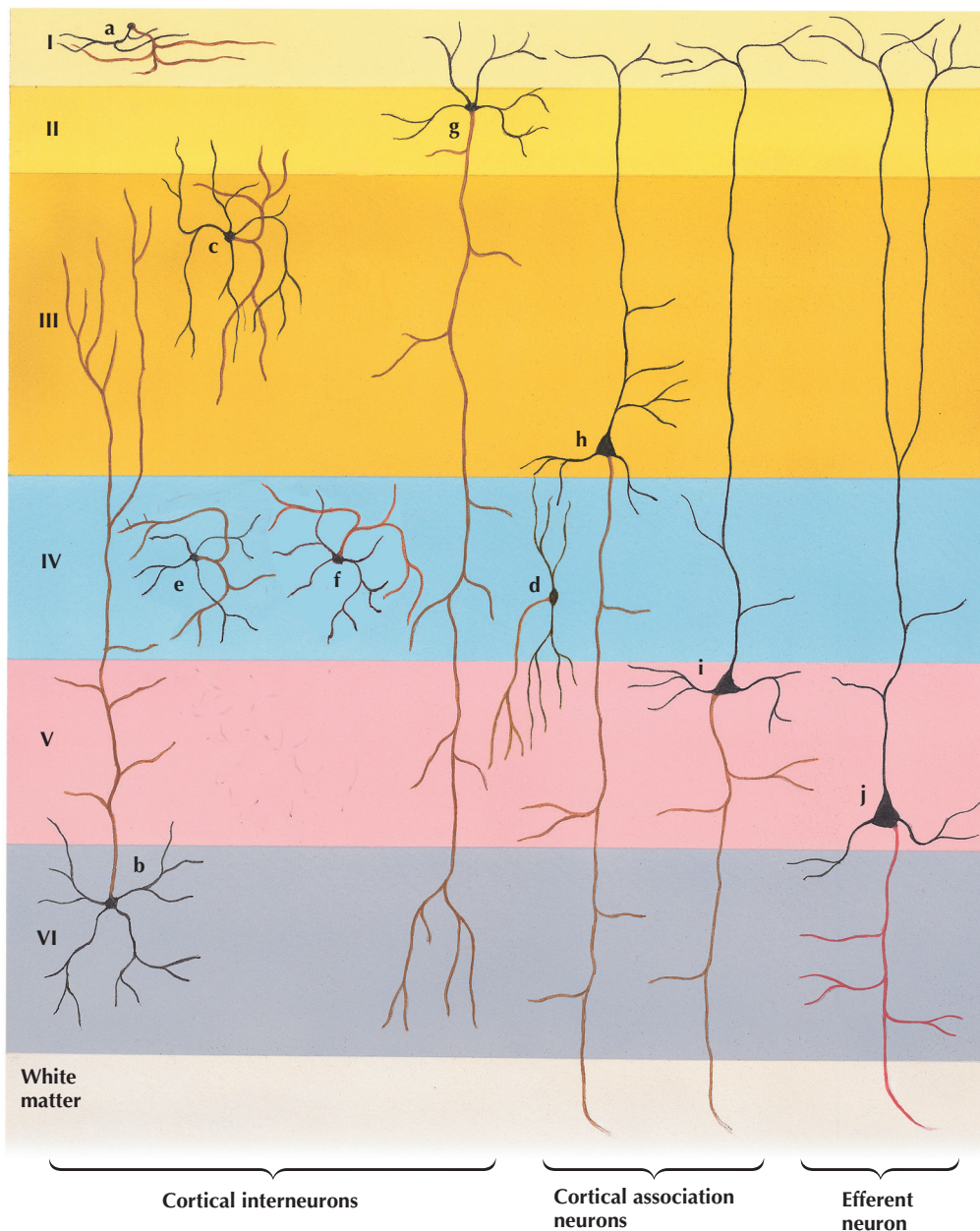


### 13.21 LAYERS OF THE CEREBRAL CORTEX

Regions of cerebral cortex with specific functional roles, such as the somatosensory cortex and the motor cortex, demonstrate histological characteristics that reflect that function. The sensory cortex has large granule cell layers (granular cortex) for receiving extensive input, whereas the motor cortex has sparse granule cell layers and extensive pyramidal cell

layers, reflecting extensive output. Specific and nonspecific afferents terminate differentially in these structurally unique regions of the cortex. Monoamine inputs (noradrenergic and serotonergic) terminate more diffusely than do the specific inputs, reflecting the role of monoamines as modulators and enhancers of the activity of other neuronal systems.

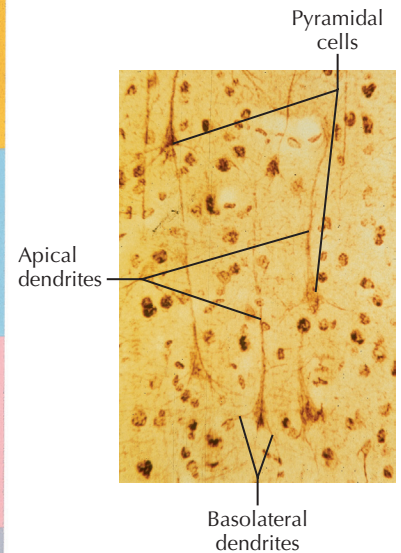




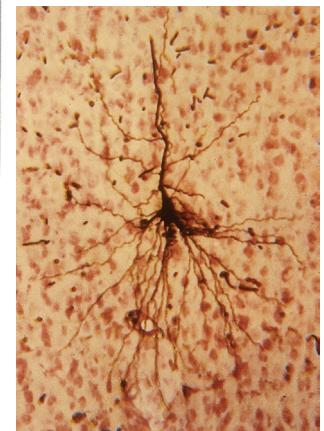
Black—cell bodies and dendrites  
Brown—axons of interneurons and association neurons  
Red—axon of efferent neurons

#### Key for Abbreviations

- a Horizontal cell
- b Cell of Martinotti
- c Chandelier cell
- d Aspiny granule cell
- e Spiny granule cell
- f Stellate (granule) cell
- g Small pyramidal cell of layers II, III
- h Small pyramidal association cell
- i Small pyramidal association and projection cells of layer V
- j Large pyramidal projection cell (Betz cell)



Multiple cortical pyramidal cells with conspicuous apical dendrites and basolateral dendrites, and other cortical cells. Fiber stain.

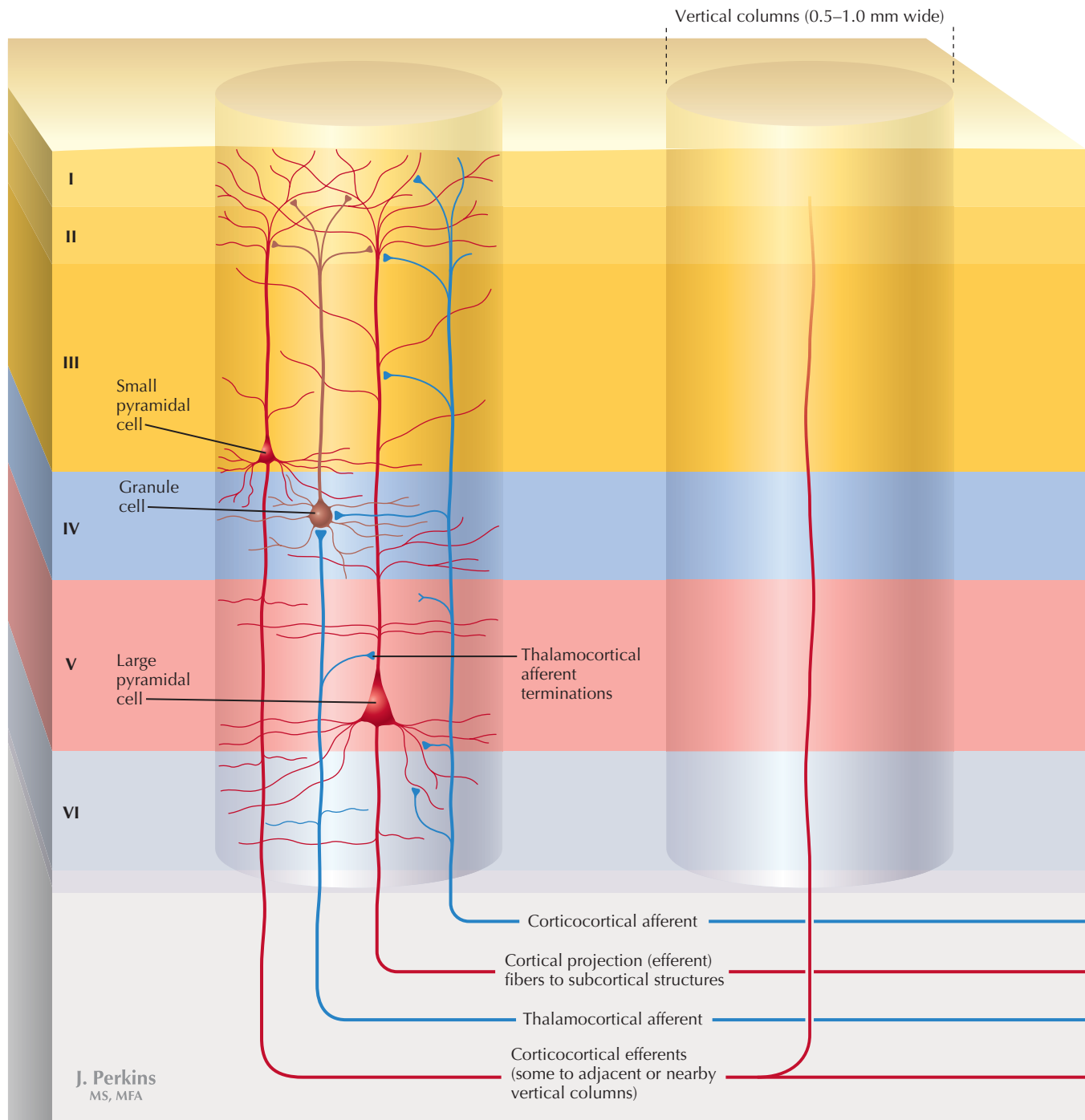


Pyramidal neuron with massive dendritic branching, particularly the basolateral dendrites. Golgi stain with background cell stain.

### 13.22 CORTICAL NEURONAL CELL TYPES

The cerebral cortex has many anatomically unique cell types that have characteristic cell bodies, dendritic arborizations, and axonal distributions. Granule cells are local circuit neurons with small cell bodies, localized dendritic trees, and axons that distribute locally. Granule cells function as receiving neurons for thalamic and other inputs, and they modulate the excitability of other cortical neurons. Pyramidal cells possess more varied cell bodies (some large, some small) that have large

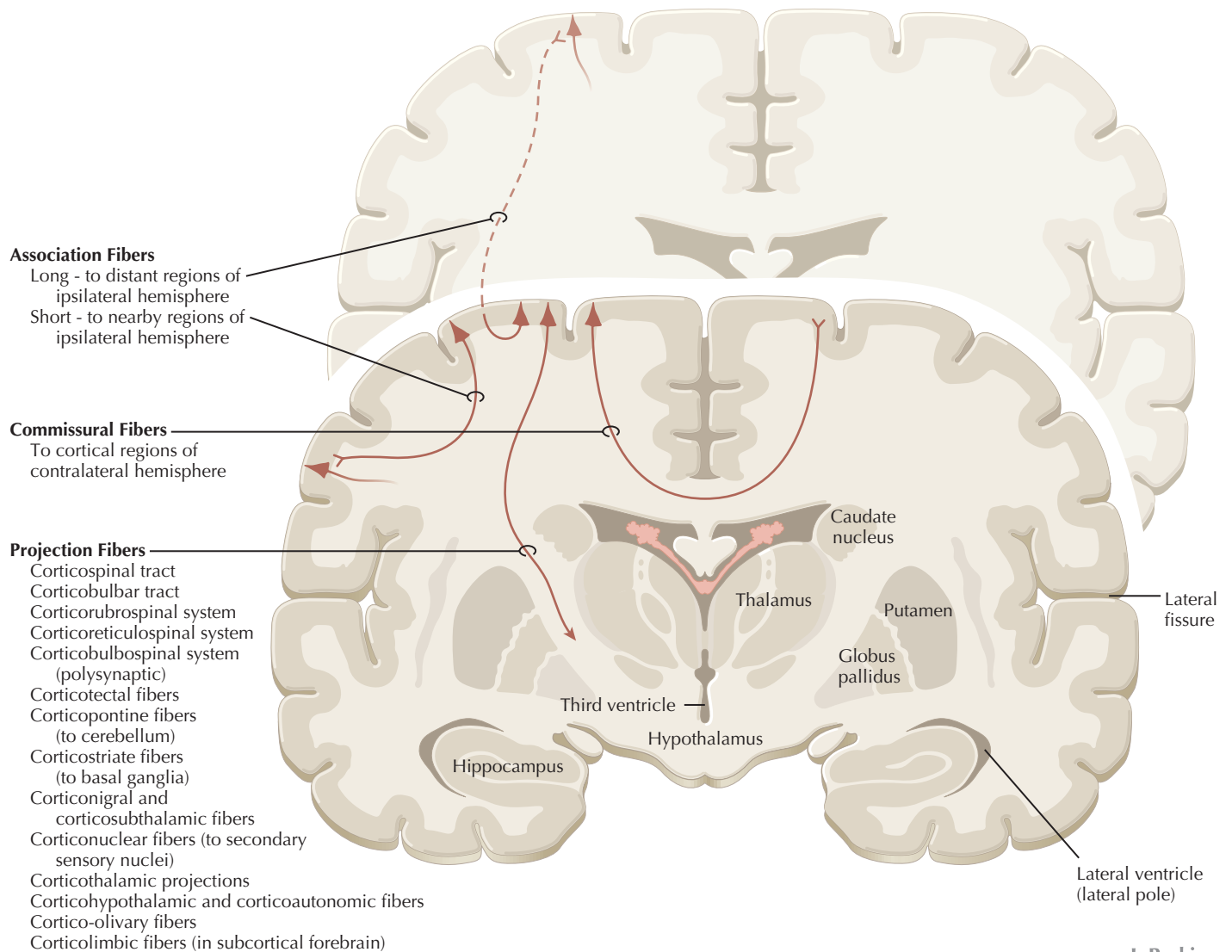
basolateral dendritic branching patterns and apical dendritic arborizations that run perpendicular to the cortical surface and arborize in upper layers. The axons of pyramidal cells, which function as projection neurons (e.g., corticospinal tract neurons), leave the cortex and may extend for as long as a meter before synapsing on target neurons. These unique anatomical characteristics give rise to the concept that neuronal structure explains neuronal function.



### 13.23 VERTICAL COLUMNS: FUNCTIONAL UNITS OF THE CEREBRAL CORTEX

Experimental studies of sensory regions of the cerebral cortex provided anatomical and physiological evidence that discrete information that comes from a specific region or that conveys specific functional characteristics is processed in a cylindrical vertical zone of neurons in the cortex that spans all six layers of the neocortex. These vertical units vary from 0.5 to 1.0 mm in diameter. The diameter corresponds to the major horizon-

tal expanse of a larger pyramidal cell in that unit. Both thalamic and cortical afferents arborize in the vertical column and synapse on both stellate (granule) cells and pyramidal neuron dendrites. Information from a vertical column can be sent to an adjacent or nearby column via corticocortical efferents or can be sent to distant structures by commissural fibers (cortex on the other side) or by projection fibers (subcortical structures). The minimal elements of the vertical unit are shown.



J. Perkins  
 MS, MFA

### 13.24 EFFERENT CONNECTIONS OF THE CEREBRAL CORTEX

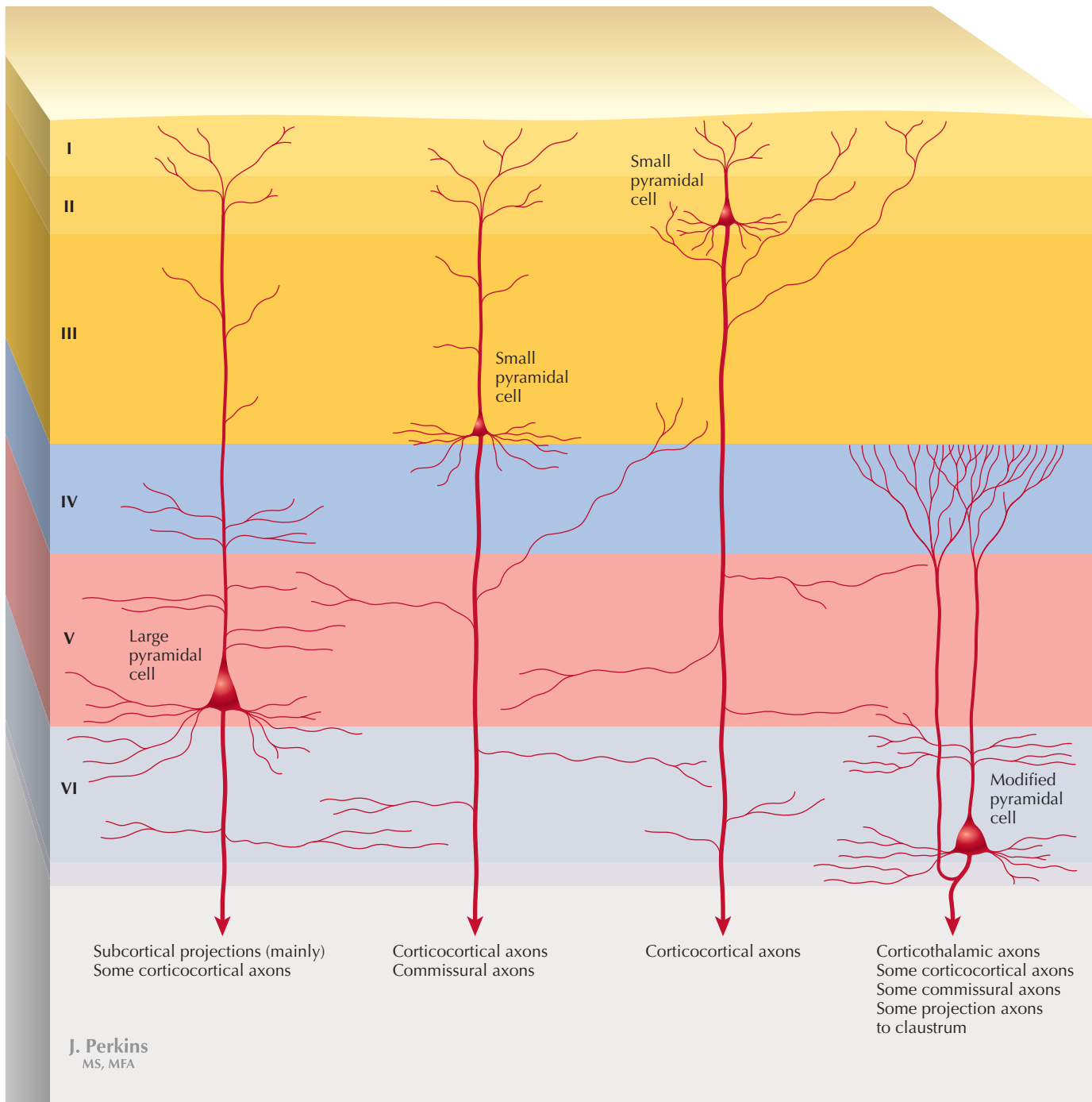
Neurons of the cerebral cortex send efferent connections to three major regions: (1) association fibers are sent to other cortical regions of the same hemisphere, either nearby (short-association fibers) or at a distance (long-association fibers); (2) commissural fibers are sent to cortical regions of the other hemisphere through the corpus callosum or the anterior commissure; and (3) projection fibers are sent to numerous subcortical structures in the telencephalon, diencephalon, brain stem, and spinal cord. The major sites of termination of these connections are listed in the diagram.

#### CLINICAL POINT

The cerebral cortex provides the highest level of regulation over motor and sensory systems, behavior, cognition, and the functional capaci-

ties of the brain that are most characteristic of human accomplishment. The cortex does this through three types of efferent pathways: (1) association fibers; (2) commissural fibers; and (3) projection fibers. Association fibers interconnect with either nearby (short) or distant (long) regions of cortex. Damage to long-association fibers can disconnect regions of cortex that normally need to communicate; this can result in altered language function, altered behavior, and other cortex-related problems. Damage to commissural fibers, especially the corpus callosum and anterior commissure, sometimes done deliberately to alleviate the spread of seizure activity, can result in a disconnection between the left and right hemispheres, with each hemisphere not being fully aware of what the other is doing because it does not have separate input. Damage to the projection fibers, which commonly accompanies infarcts or lesions in the internal capsule, can disrupt cortical outflow to the spinal cord, brain stem, cerebellum, thalamus and hypothalamus, basal ganglia, and limbic forebrain structures. As a consequence, major sensory deficits (especially in the opposite side for somatic sensation and vision), contralateral spastic hemiplegia with central facial involvement, hemianopia, and other motor, sensory, and behavioral deficits may occur.

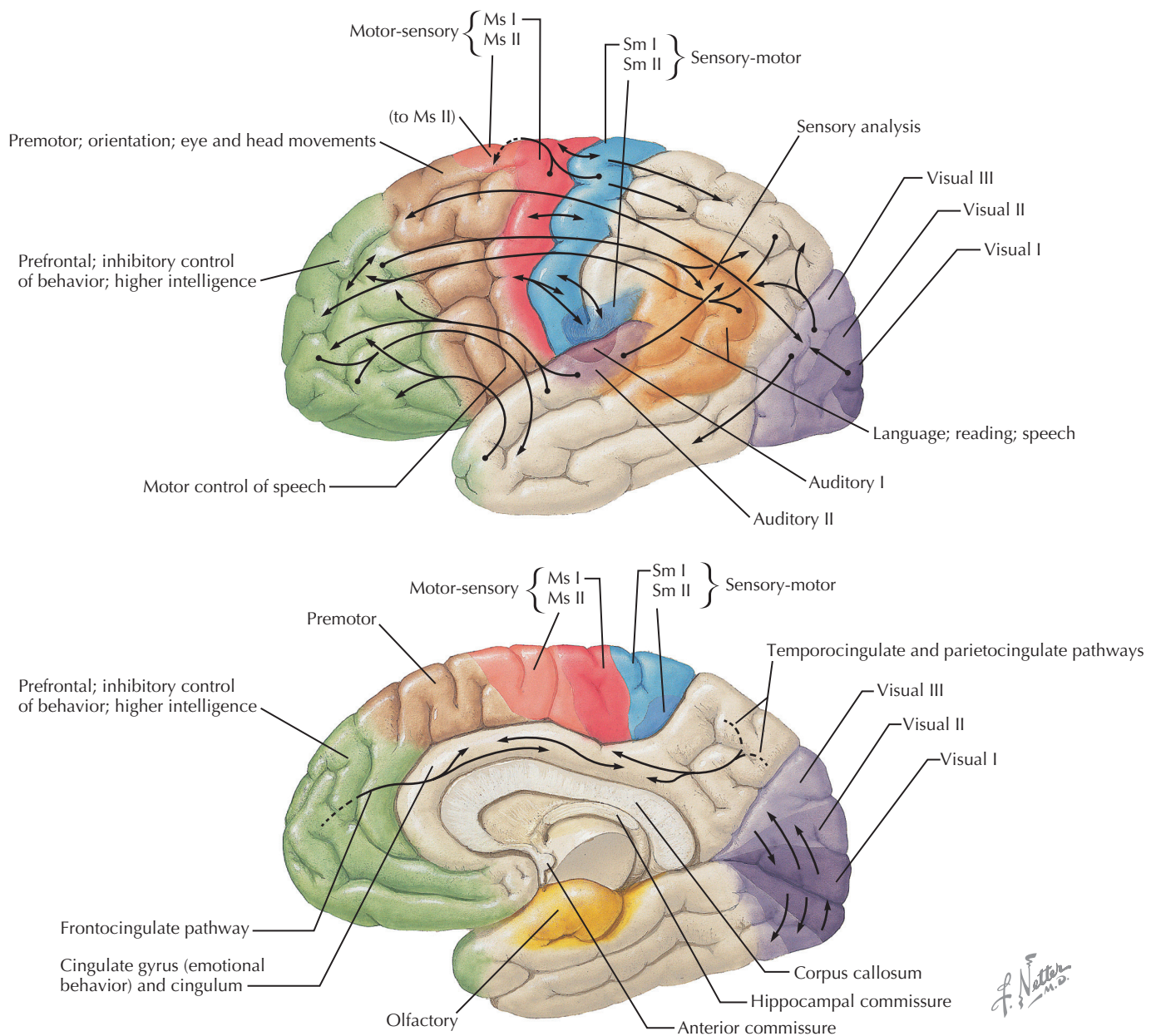




### 13.25 NEURONAL ORIGINS OF EFFERENT CONNECTIONS OF THE CEREBRAL CORTEX

Association fibers destined for cortical regions of the same hemisphere arise mainly from smaller pyramidal cells in cortical layers II and III and from modified pyramidal cells in layer VI. Commissural fibers destined for cortical regions of the

opposite hemisphere arise mainly from small pyramidal cells in cortical layer III and from some modified pyramidal cells in layer VI. Projection fibers arise from larger pyramidal cells in layer V and also from smaller pyramidal cells in layers V and VI. Only a small number of projection fibers arise from the giant Betz cells in layer V.



### 13.26 CORTICAL ASSOCIATION PATHWAYS

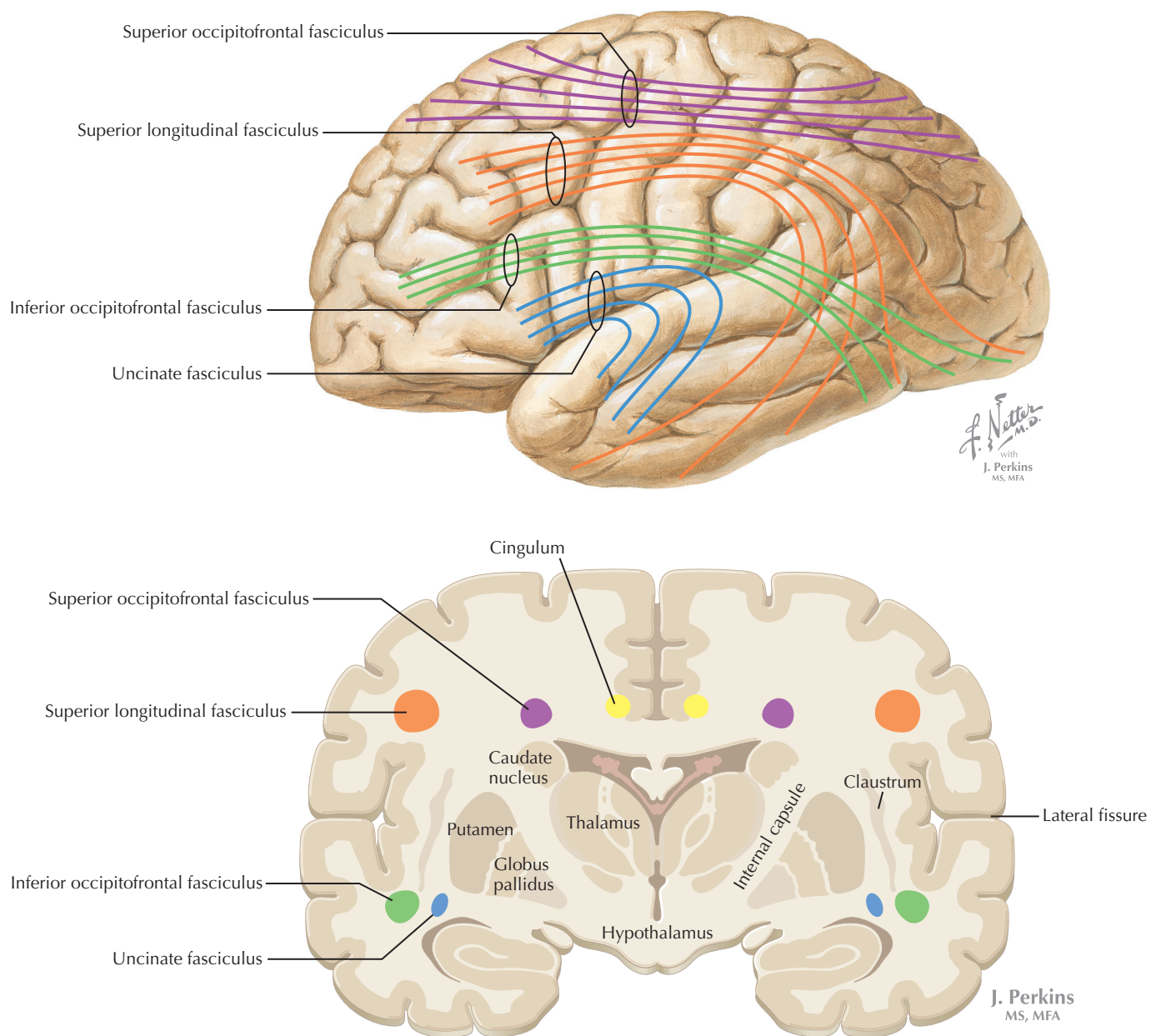
Neurons of the cerebral cortex have extensive connections with other regions of the brain (projection neurons); with the opposite hemisphere (commissural neurons); and with other regions of the ipsilateral hemisphere (association fibers). The cortical association fibers may connect a primary sensory cortex with adjacent association areas (e.g., visual cortex, somatosensory cortex) or may link multiple regions of cortex into complex association areas (e.g., polysensory analysis regions) or interlink important areas involved in language function, cognitive function, and emotional behavior and analysis. Damage to these pathways and associated cortical regions can result in loss of specific sensory and motor capabilities, aphasia (language disorders), agnosias (failures of recognition), and apraxias (performance deficits).

#### CLINICAL POINT

Long cortical association pathways link regions of cortex with each other. Some pathways link multiple sensory areas with multimodal cortical association cortex, providing the substrate for integrated interpretation of the outside world. Some association pathways

connect language areas in the dominant hemisphere with each other. Broca's area of the frontal cortex and Wernicke's area in the parieto-temporal region are interconnected by long-association fibers of the arcuate fasciculus or superior longitudinal fasciculus. When these association fibers are damaged, Broca's area and Wernicke's area are disconnected. The patient does not demonstrate a classic expressive or receptive aphasia but demonstrates the inability to repeat complex words or sentences. This is called conduction aphasia.

Subcortical white matter plays an important role in human behavior. Many types of pathology can affect subcortical white matter such as multi-infarct damage or demyelination. These conditions cause a disconnection between regions of cerebral cortex or between subcortical regions and cortex. With multiple regions of white matter damage, dementia can occur, including inattention, emotional changes, and memory problems; such changes generally occur in the absence of movement disorders or aphasia. Multi-infarct damage to the ascending catecholamine and serotonin pathways from the brain stem can occur with destruction of the axons in the cingulum, resulting in depression and bipolar disorder, as well as attention deficits, especially with lesions involving ascending noradrenergic and reticular activating circuitry. Bilateral damage to white matter of the frontal lobe may result in euphoria and inappropriate affect, whereas damage to the long-association fibers interconnecting the frontal lobes with limbic forebrain structures may result in psychotic behavior.



### 13.27 MAJOR CORTICAL ASSOCIATION BUNDLES

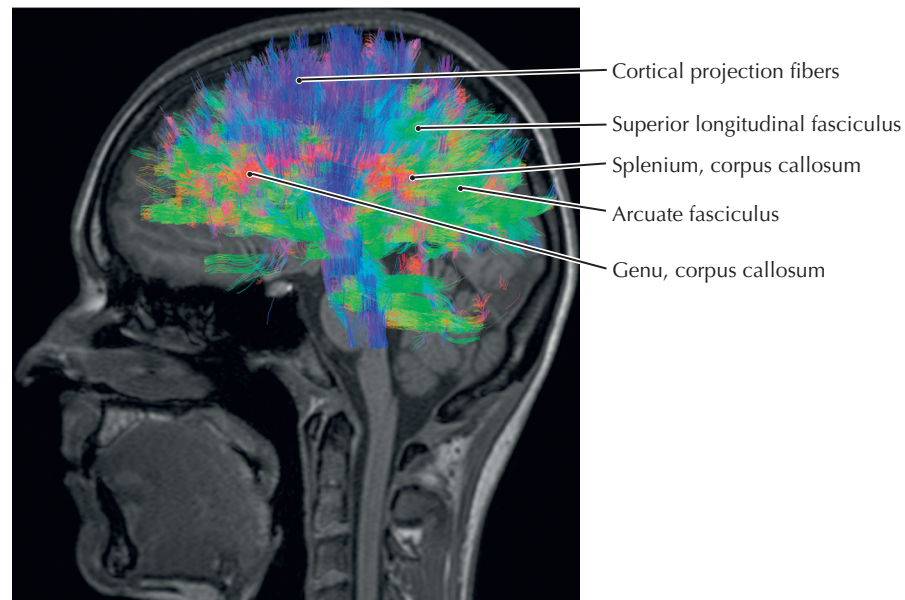
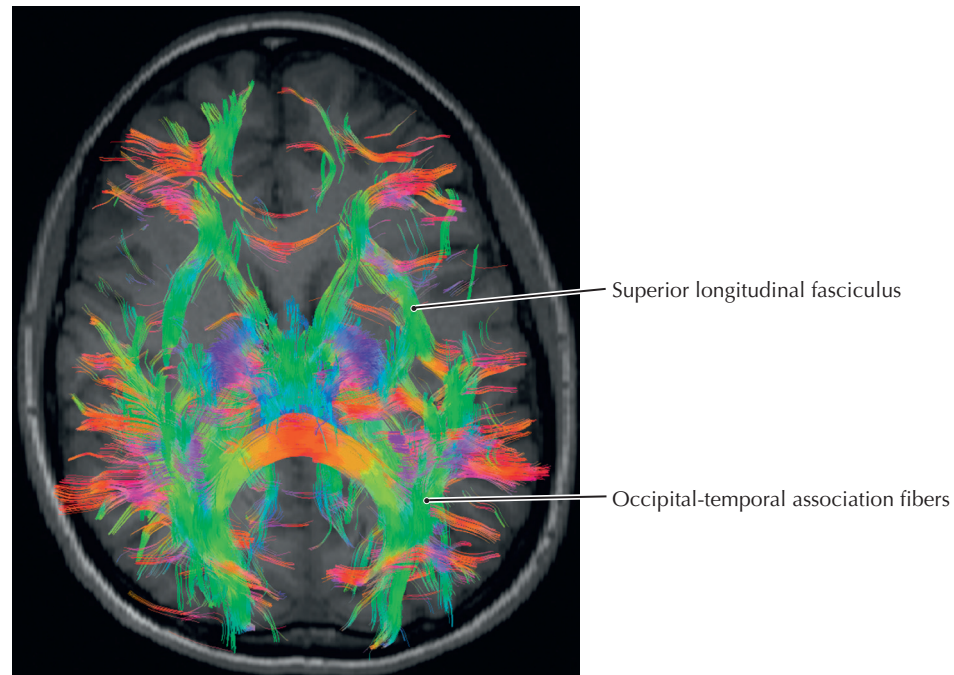
Association fibers interconnecting cortical regions in one hemisphere with adjacent or distant regions of the same hemisphere are categorized as short-association fibers (arcuate fibers) or long-association fibers. The long-association fibers often are recognized anatomically as specific association bundles and may have numerous fiber systems entering, exiting, and traversing them. Important named bundles include the uncinate fasciculus, the superior longitudinal fasciculus, the superior and inferior occipitofrontal fasciculi, and the cingulum. The cingulum is a bundle through which the major monoamines (dopamine, norepinephrine, serotonin) and part of the cholinergic projections travel to their widespread target sites.

#### CLINICAL POINT

Cortical association pathways, or bundles, can become demyelinated in multiple sclerosis and other demyelinating diseases, leading to cognitive and emotional problems in addition to the sensory, motor, and autonomic involvement that is well known in such disorders. Diminished attention and vigilance can occur with demyelination of association pathways, and that may contribute to some of the memory impairment seen in recall tasks. Inappropriate expression of emotion and euphoria or emotional disinhibition (sometimes called pseudo-bulbar affect) can occur with damage to frontal association pathways. Both depressive and bipolar disorders occur more commonly in patients with multiple sclerosis than in controls, and there is some correlation with the presence of demyelinating lesions in the temporal lobe, although monoaminergic pathways also may be involved. Although many clinicians view some of the demyelinating plaques that form in subcortical white matter to be “silent lesions” that produce no pathology, the end point for evaluation usually has been classic motor and sensory symptoms, not emotional and cognitive dysfunction. Although such deficits may be more common than previously supposed, the ability of the brain to repair demyelinated lesions often can ameliorate such deficits.



A. Axial view



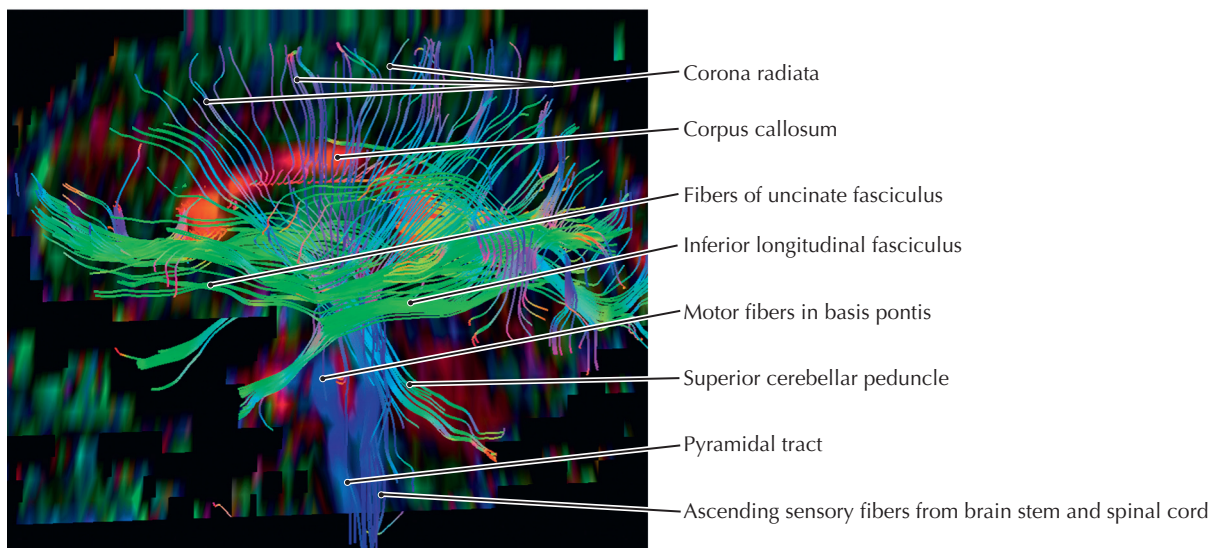
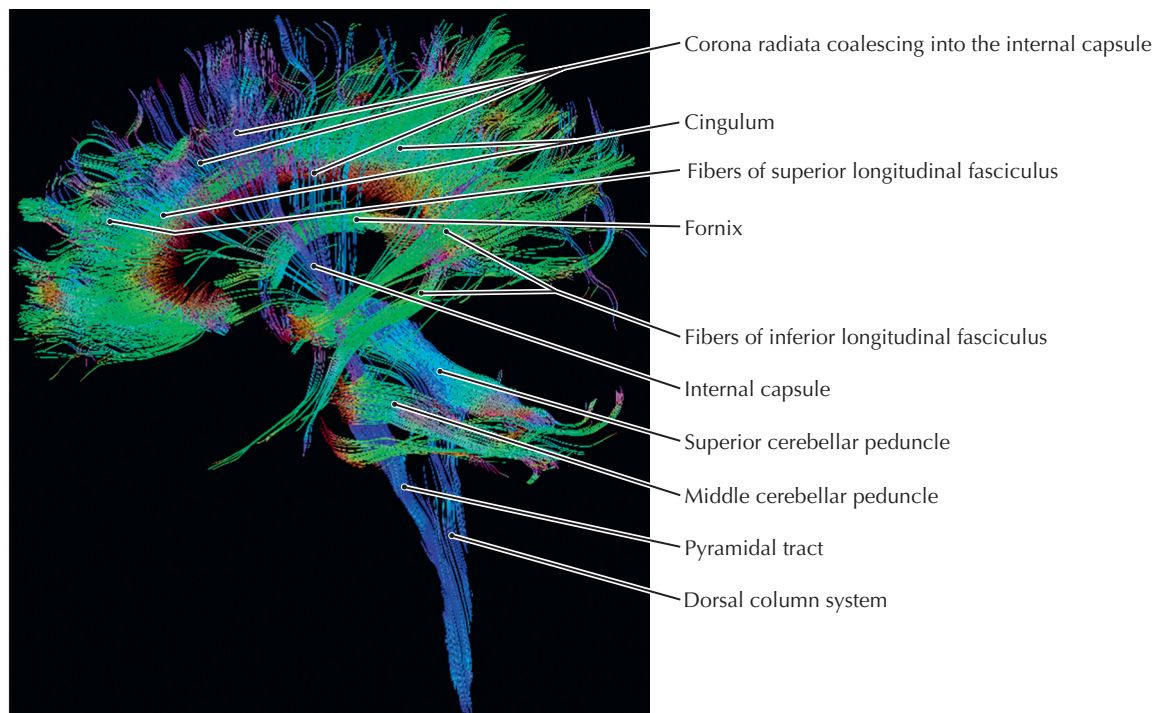
B. Sagittal view

### 13.28 COLOR IMAGING OF ASSOCIATION PATHWAYS

These diffusion tensor images show the association pathways of the forebrain in green (anterior-posterior direction) in an axial section and in a sagittal section. The most conspicuous

association fibers in these images are the long-association pathways. Commissural fibers appear red/orange (left-right direction), and projection fibers appear blue (superior-inferior direction).

## A. Sagittal view

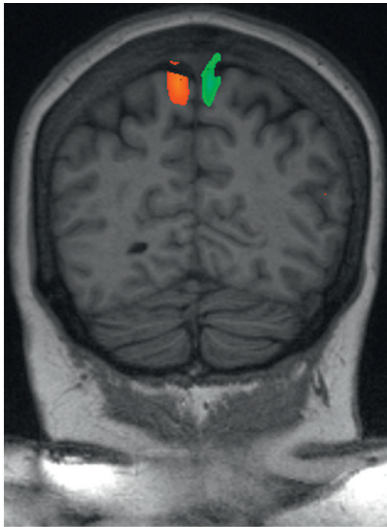


## B. Sagittal view

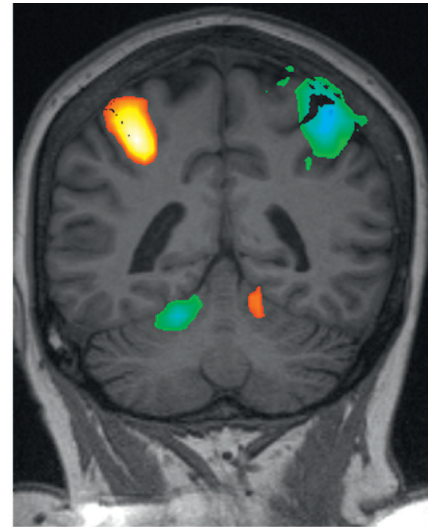
### 13.29 COLOR IMAGING OF PROJECTION PATHWAYS FROM THE CEREBRAL CORTEX

These diffusion tensor images show the projection pathways of the forebrain in blue in two sagittal sections. The widespread cortical projection bundles channel into a narrow zone

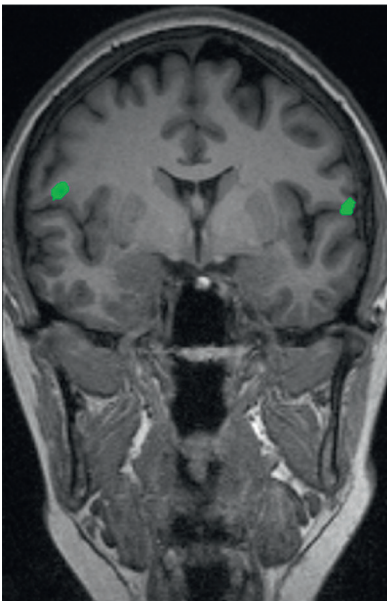
of the internal capsule and then proceed to their sites of projection in the forebrain, brain stem, or spinal cord. The descending corticospinal/corticobulbar system is particularly prominent. Projection systems associated with the cerebellum also are present. In addition, green association fibers and red commissural fibers also can be seen. See [Videos 13-3 and 13-4](#).



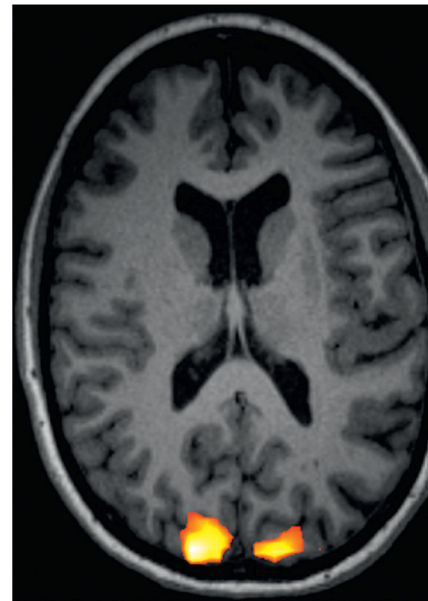
**A.** Coronal section showing midline motor cortex response to alternating movement of the toes.



**B.** Coronal section showing contralateral convexity motor cortex response and ipsilateral cerebellar response to rapid alternating sequential tapping movement of the fingers bilaterally.



**C.** Coronal section showing Broca's area response to a language task in which subjects must silently discriminate word characteristics as abstract, concrete, single, double, upper case, or lower case over a 30-second time span.













**D.** Axial section showing occipital cortex response to a visual task of viewing flickering alternating bands on a screen.

### 13.30 FUNCTIONAL MAGNETIC RESONANCE IMAGING

Functional magnetic resonance imaging (fMRI) is a non-invasive method that uses no radioactive tracers; it takes advantage of the fact that there is a difference in magnetic states of arterial and venous blood, thus providing an intrinsic mechanism of contrast for brain activation studies. The origin of this dual state of blood is due to the fact that the magnetic state of hemoglobin (Hb) depends on its oxygenation; the oxyhemoglobin state (arterial blood) is diamagnetic, and the venous deoxyhemoglobin state (venous blood) is paramagnetic. The change in oxygen saturation of the hemoglobin produces a detectable small signal change; hence, it is called the blood oxygenation level-dependent (BOLD) effect.

During neural activity, the supposition behind BOLD-fMRI is that the involved neurons represent a region of relatively greater oxygenated hemoglobin compared with non-active regions in T2\*-weighted images. However, there is a delay of several seconds between increased neural activity and increased oxygenated arterial blood flow to that region. BOLD-fMRI compares images during specific activity to images of the same region without such activity and can be used for processes that occur rapidly, such as language function, vision, audition, movement, cognitive tasks, and emotional responsiveness. The above images are taken from a sequence of coronal and axial sections showing regions of brain that are activated during A) movement of toes, B) sequential finger tapping, C) language task, and D) visual stimulation.

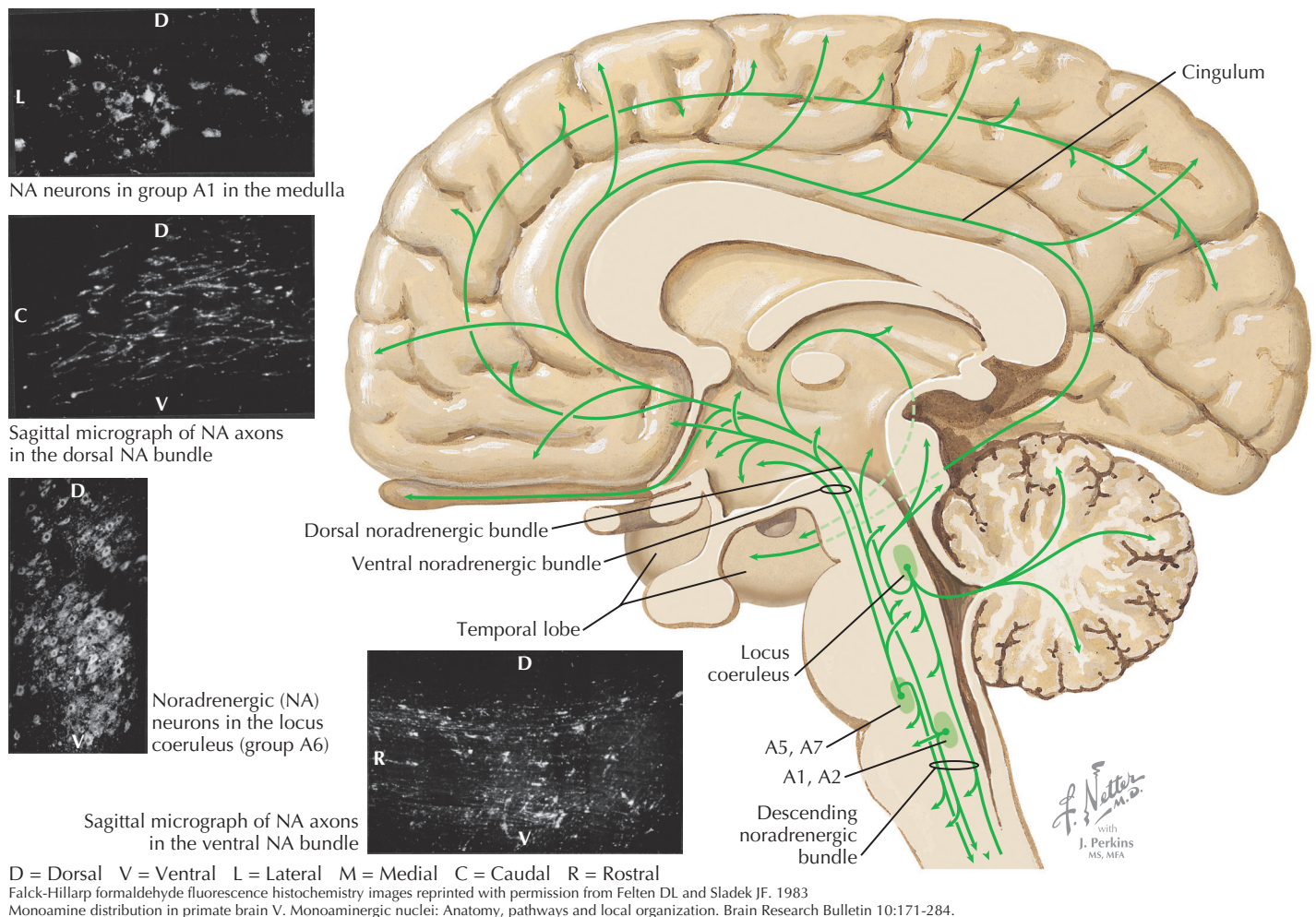


Infarct, surface	Infarct, coronal section	Clinical manifestations
		<p><b>Broca aphasia (if on left side)</b> Contralateral hemiplegia, hemisensory loss, gaze palsy, spatial neglect</p>  <p>Patient trying to find words but only producing nonfluent effortful, slow, halting speech</p>
		<p><b>Wernicke aphasia (if on left side)</b> Contralateral hemianopsia or upper quadrantanopsia Constructional dyspraxia (if on right side)</p>  <p>Fluent phonemic mixed syllables verbally incorrect words (i.e., paraphrase errors/ "word salad")</p>
 		<p><b>Global aphasia (if on left side)</b> Contralateral gaze palsy, hemiplegia, hemisensory loss, spatial neglect, hemianopsia May lead to decreased consciousness and even coma secondary to edema</p>  <p>Right-handed patient with severe hemisphere deficit unable to utter any language or comprehend with hemiplegia individual</p>

13.31 APHASIAS AND CORTICAL AREAS OF DAMAGE

Cerebral infarcts and other damage to cortical gray matter and cortical white matter (long association pathways) can result in language disorders, called aphasia. This chart presents the

location and clinical manifestations of major types of aphasia, including Broca (expressive) aphasia, Wernicke (receptive) aphasia, and global aphasia. The location and clinical characteristics of conduction aphasia are discussed in [13.26 Clinical Point](#).



### 13.32 NORADRENERGIC PATHWAYS

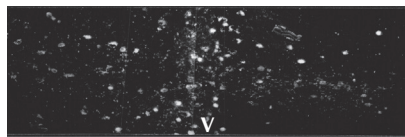
Noradrenergic neurons in the brain stem project to widespread areas of the central nervous system (CNS). The neurons are found in the locus coeruleus (group A6) and in several cell groups in the reticular formation (RF; tegmentum) of the medulla and pons (A1, A2, A5, and A7 groups). Axonal projections of the locus coeruleus branch to the cerebral cortex, hippocampus, hypothalamus, cerebellum, brain stem nuclei, and spinal cord. The locus coeruleus acts as a modulator of the excitability of other projection systems such as the glutamate system and helps to regulate attention and alertness, the sleep-wake cycle, and appropriate responses to stressors, including pain. The RF groups are interconnected extensively with the spinal cord, brain stem, hypothalamic, and limbic regions involved in neuroendocrine control, visceral functions (temperature regulation, feeding and drinking behavior, reproductive behavior, autonomic regulation) and with emotional behavior. Serotonergic neurons of the raphe system overlap with many of these noradrenergic connections, and comodulate related functional activities. A sparse set of epinephrine-containing neurons in the medullary RF are similarly interconnected. These RF noradrenergic neurons can work in concert with the locus coeruleus during challenge or in response to a stressor to coordinate alertness and appropriate neuroendocrine and autonomic responsiveness. The central noradrenergic and adrenergic neurons and their receptors are the targets of many pharmacological agents, including those that target depression, analgesia, hypertension, and many other conditions.

### CLINICAL POINT

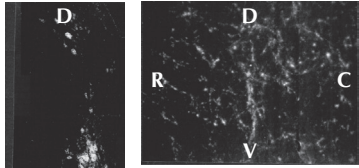
The axonal projections of the brain stem noradrenergic cell groups have incredibly widespread distribution to virtually all subdivisions of the CNS. The locus coeruleus acts as a modulator of the excitability of other axonal systems and can augment both glutamate excitability and gamma aminobutyric acid (GABA) inhibition within the same neurons (Purkinje cells). In keeping with such a modulatory role, the locus coeruleus system appears to help regulate attention, alertness, and sleep-wakefulness cycles. Similarly, the brain stem tegmental noradrenergic systems have projections to spinal cord, brain stem, hypothalamic, and limbic regions and help to regulate neuroendocrine outflow and visceral functions, such as feeding, drinking, reproductive behavior, and autonomic regulation. In the spinal cord, descending noradrenergic projections modulate the excitability of lower motor neurons in the ventral horn.

Central noradrenergic forebrain projections also influence emotional behavior and are integral to the catecholamine hypothesis of affective disorders, especially depression. Depression is hypothesized to be the result of diminished functioning of central noradrenergic connections (although serotonergic dysfunction is probably involved as well). All three major classes of drugs used for treating depression (monoamine oxidase inhibitors, tricyclic antidepressants, and psychomotor stimulants) enhance noradrenergic neurotransmission. MHPG (3-methoxy-4-hydroxyphenylglycol), the major metabolite of central norepinephrine, is diminished in many depressed individuals. As a phenomenon accompanying depression, the altered noradrenergic activity in the brain of depressed patients may exert a regulatory impact on the ability of the paraventricular nucleus of the hypothalamus to activate the stress axes, accounting for the increased cortisol and peripheral catecholamine secretion seen in many depressed individuals.





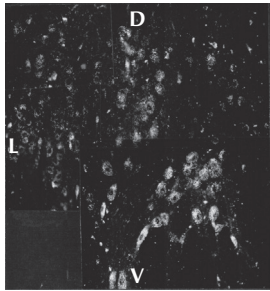
Serotonergic neurons in nucleus raphe obscurus and in lateral wings of cells that extend into the adjacent reticular formation



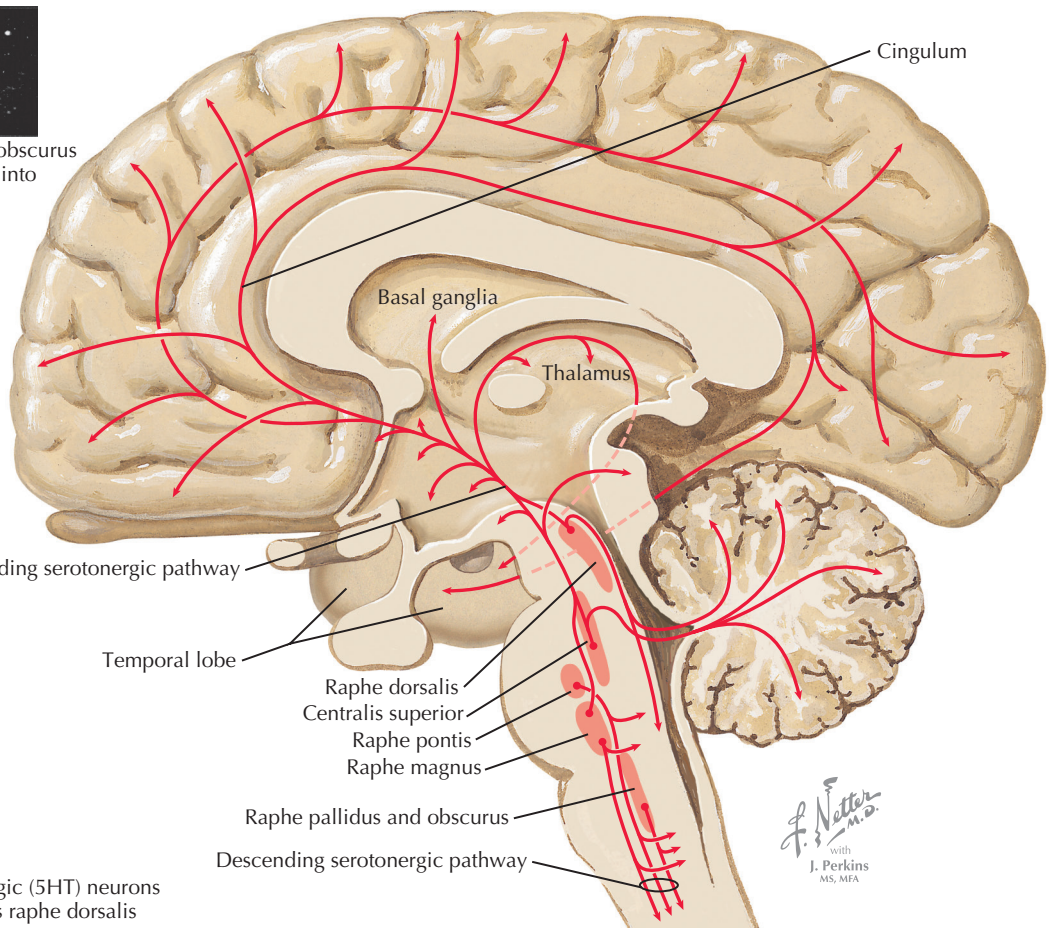
Sagittal micrograph of 5HT axons in the ascending serotonergic pathway



Serotonergic neurons in nucleus raphe pontis



Serotonergic (5HT) neurons in nucleus raphe dorsalis



D = Dorsal V = Ventral L = Lateral M = Medial C = Caudal R = Rostral

Falck-Hillarp formaldehyde fluorescence histochemistry images reprinted with permission from Felten DL and Sladek JF. 1983

Monoamine distribution in primate brain V. Monoaminergic nuclei: Anatomy, pathways and local organization. Brain Research Bulletin 10:171-284.

### 13.33 SEROTONERGIC PATHWAYS

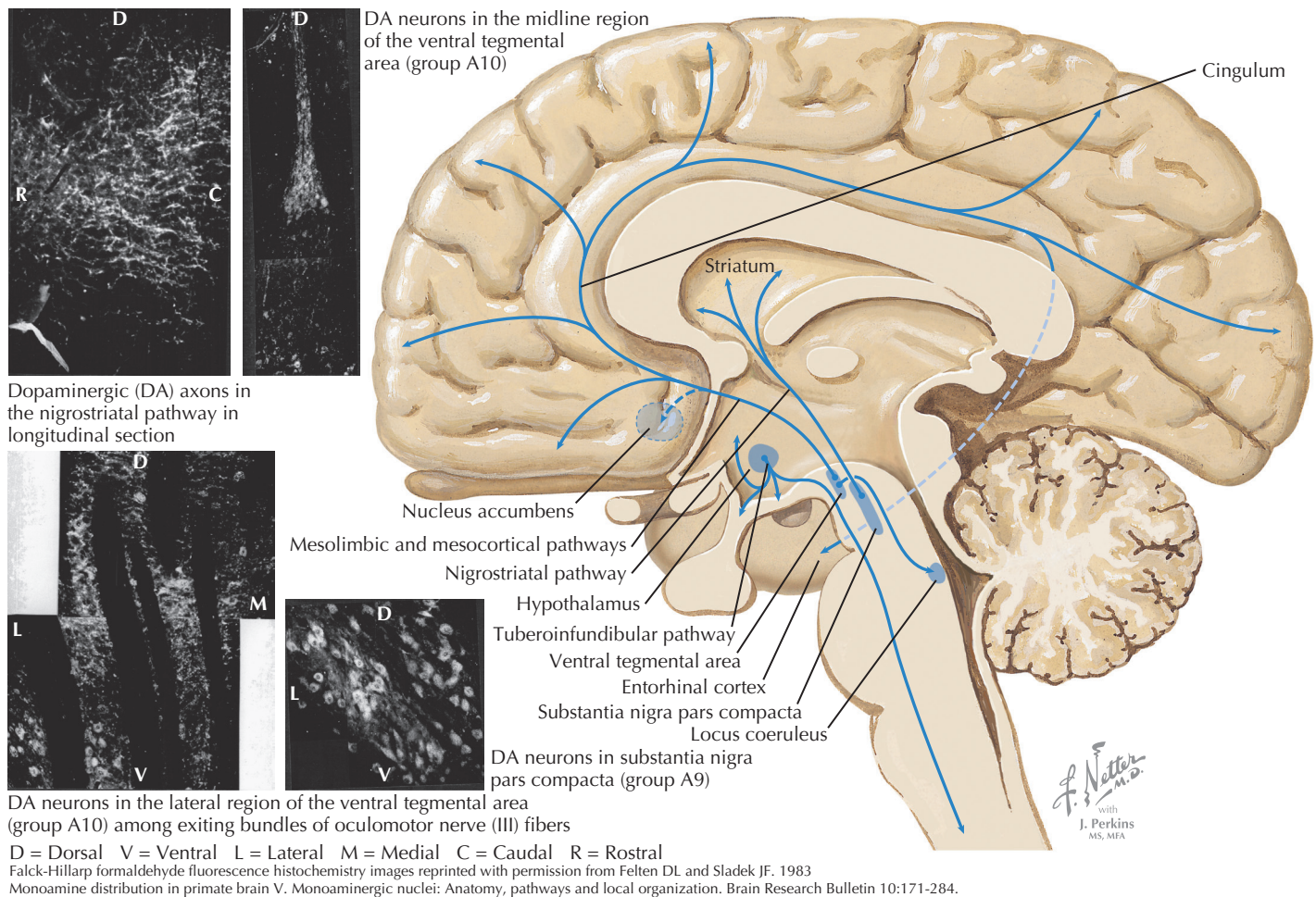
Serotonergic neurons (5-hydroxytryptamine; 5-HT), found in the raphe nuclei of the brain stem and adjacent wings of cells in the RF, have widespread projections that innervate every major subdivision in the CNS. The rostral serotonergic neurons in nucleus raphe dorsalis and centralis superior project rostrally to innervate the cerebral cortex, many limbic forebrain structures (hippocampus, amygdala), the basal ganglia, many hypothalamic nuclei and areas, and some thalamic regions. The caudal serotonergic neurons in the nuclei raphe magnus, pontis, pallidus, and obscurus project more caudally to innervate many brain stem regions, the cerebellum, and the spinal cord. Of particular importance are the projections of the nucleus raphe magnus to the dorsal horn of the spinal cord, at which site opiate analgesia and pain processing are markedly influenced. The ascending serotonergic systems are involved in the regulation of emotional behavior and wide-ranging hypothalamic functions (neuroendocrine, visceral/autonomic), similar to their noradrenergic counterparts. Serotonergic neurons are involved in sleep-wakefulness cycles and, like locus coeruleus noradrenergic neurons, stop firing during rapid-eye-movement sleep. Serotonergic projections to the cerebral cortex modulate the processing of afferent inputs (e.g., from the visual cortex). The descending serotonergic neurons enhance the effects of analgesia and are essential for opiate analgesia. They also modulate pregangli-

onic autonomic neuronal excitability and enhance the excitability of lower motor neurons. Many pharmacological agents target serotonergic neurons and their receptors, including drugs for treating depression, other cognitive and emotional behavioral states, headaches, pain, some movement disorders, and other conditions.

#### CLINICAL POINT

Serotonergic neurons of the raphe nuclei and adjacent reticular formation have incredibly widespread projections to virtually all subdivisions of the CNS, similar to the brain stem noradrenergic neurons. Serotonergic systems can modulate the excitability of other neural systems and are involved in the regulation of emotional behavior, neuroendocrine secretion and circadian rhythms, and widespread visceral functions (e.g., food intake, pain sensitivity, sexual behavior, and sleep-wake cycles). During rapid-eye-movement (REM) sleep, some raphe neurons cease their electrical firing. Many early physiological studies of the serotonergic and noradrenergic systems revealed that both systems help to regulate many of the same functions. Serotonin systems have been implicated in some patients with depression. Early consideration of tricyclic antidepressants focused on their ability to block reuptake of norepinephrine, but some of the most efficacious tricyclic compounds also blocked the reuptake of serotonin. The discovery of serotonin-specific reuptake inhibitors such as fluoxetine led to their use for depression; they are therapeutically successful in a subset of individuals with major (unipolar) depression. It is not surprising that some side effects of their enhancing effects on central serotonin activity include diminished libido and eating disorders involving significant weight gain.





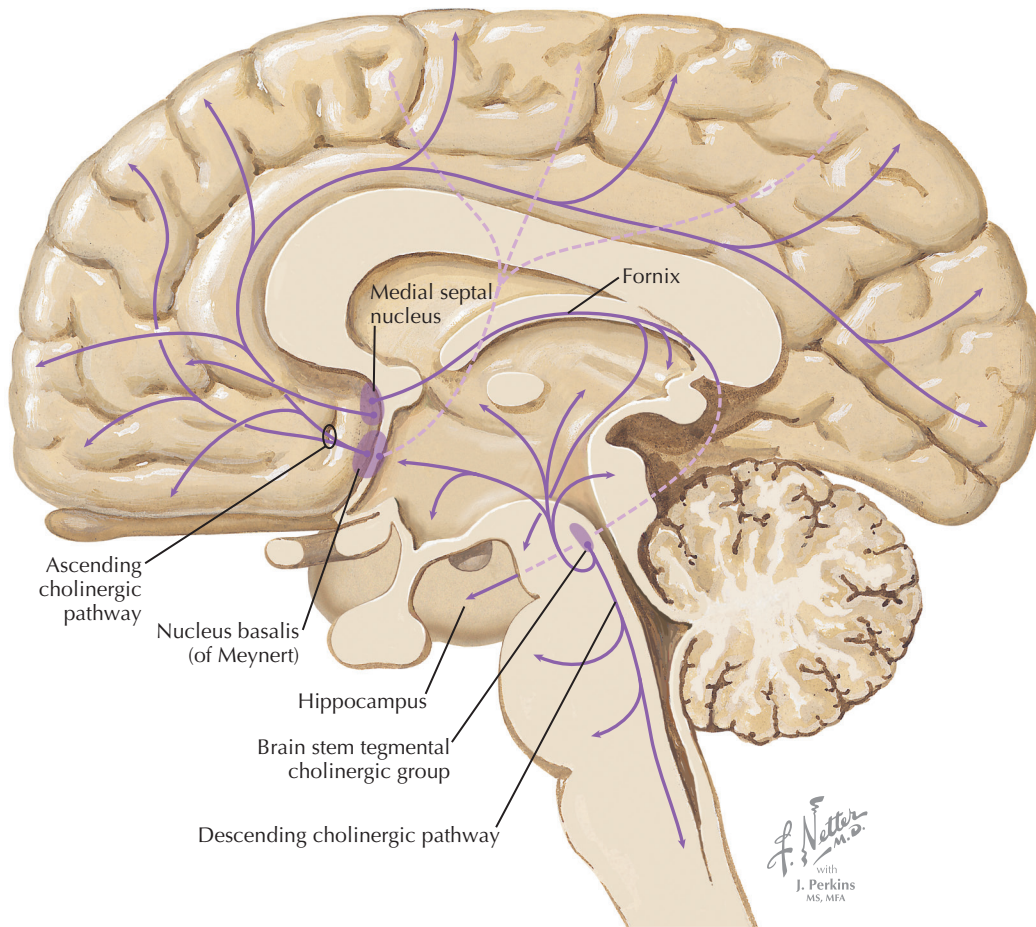
### 13.34 DOPAMINERGIC PATHWAYS

DA neurons are found in the midbrain and hypothalamus. In the midbrain, neurons in the substantia nigra pars compacta (A9) project axons (along the nigrostriatal pathway) mainly to the striatum (caudate nucleus and putamen) and to the globus pallidus and subthalamus. This nigrostriatal projection is involved in basal ganglia circuitry that aids in the planning and execution of cortical activities, the most conspicuous of which involve the motor system. Damage to the nigrostriatal system results in Parkinson's disease, a disease characterized by resting tremor, muscular rigidity, bradykinesia (difficulty initiating movements or stopping them once they are initiated), and postural deficits. The antiparkinsonian drugs such as levodopa target this system and its receptors. Dopamine neurons in the ventral tegmental area and mesencephalic RF (A10) send mesolimbic projections to the nucleus accumbens, the amygdala, and the hippocampus, and they send mesocortical projections to the frontal cortex and some cortical-association areas. The mesolimbic pathway to the nucleus accumbens is involved in motivation, reward, biological drives, and addictive behaviors, particularly substance abuse. The DA projections to limbic structures can induce stereotyped, repetitive behaviors and activities. The mesocortical projections influence cognitive functions in the planning and carrying out of frontal cortical activities, and in attention mechanisms. The mesolimbic and mesocortical DA systems and their receptors are the targets of neuroleptic and antipsychotic agents that influence behaviors in schizophrenia, obsessive-compulsive disorder, attention deficit-

hyperactivity disorder, Tourette's syndrome, and other behavioral states. Dopamine neurons in the hypothalamus form the tuberoinfundibular dopamine pathway, which projects from the arcuate nucleus to the contact zone of the median eminence, where dopamine acts as prolactin inhibitory factor. Intrahypothalamic dopamine neurons also influence other neuroendocrine and visceral/autonomic hypothalamic functions.

#### CLINICAL POINT

Several discrete DA systems are found in the brain. The midbrain nigrostriatal DA system projects from the substantia nigra pars compacta to the striatum; these neurons degenerate in Parkinson's disease. The tuberoinfundibular and intrahypothalamic DA systems are involved in neuroendocrine regulation. A midbrain mesolimbic and mesocortical system sends widespread projections to the forebrain. The mesolimbic pathway to the nucleus accumbens regulates motivation, reward, biological drives, and addictive behaviors, playing an important role in substance abuse. Activation of this circuit can induce stereotyped, repetitive behaviors and activities. The mesolimbic and mesocortical DA systems are involved in many psychiatric disorders, including schizophrenia, obsessive-compulsive disorders, attention deficit-hyperactivity disorder, Tourette's syndrome, and other behavioral states. The use of neuroleptic and antipsychotic medications, which are D2 receptor antagonists, to treat schizophrenia led to the hypothesis that schizophrenia is related to the regulation of dopamine. The current hypothesis is that this disease may involve excessive activity in the mesolimbic DA system and a relative decrease in activity in the mesocortical DA system in the frontal lobes. Use of neuroleptic agents must be monitored carefully because chronic D2 receptor antagonism may lead to tardive dyskinesia, permanent drug-induced movements.



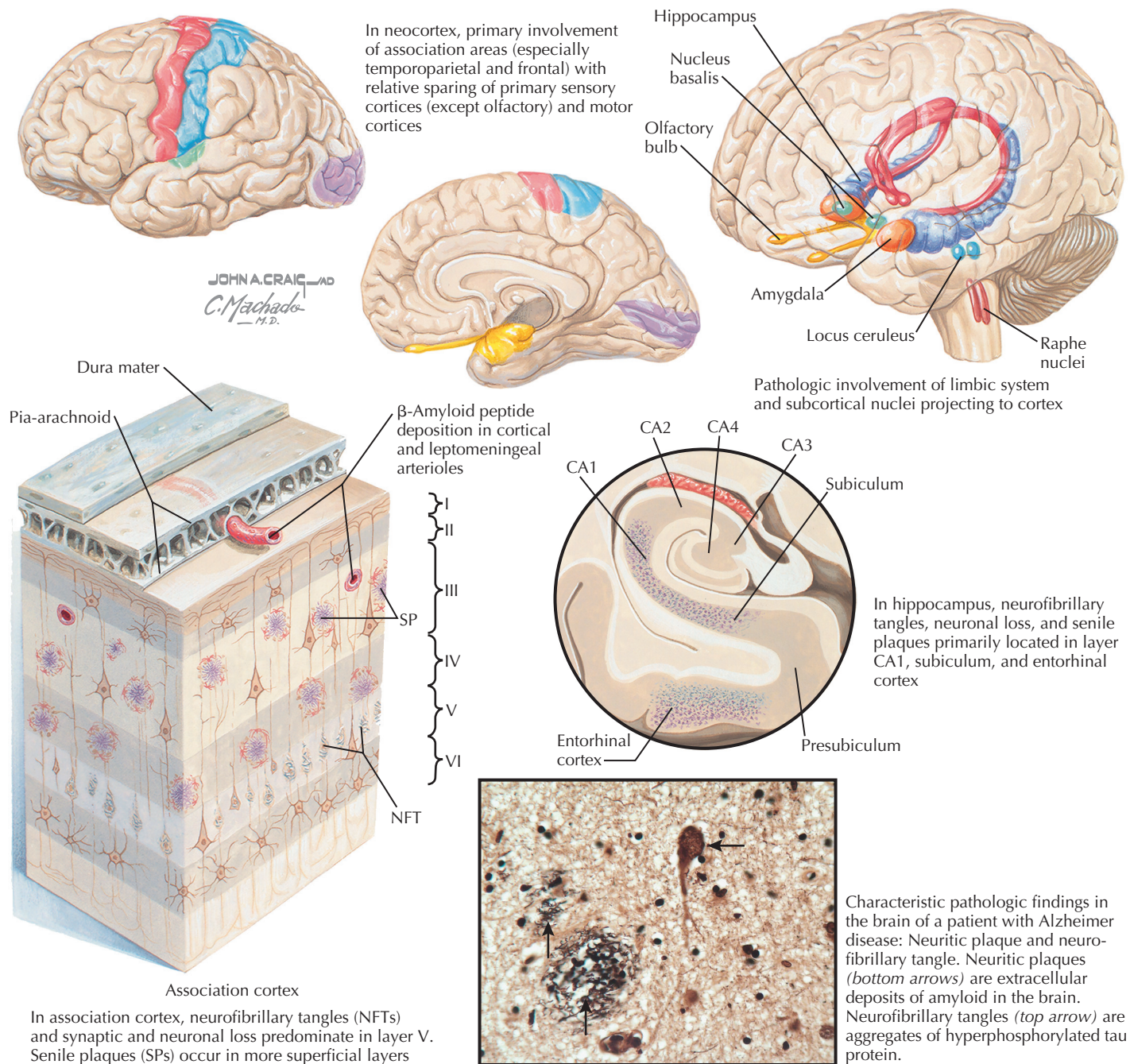
### 13.35 CENTRAL CHOLINERGIC PATHWAYS

Central cholinergic neurons are found mainly in the nucleus basalis (of Meynert) and in septal nuclei. Nucleus basalis neurons project cholinergic axons to the cerebral cortex, and the septal cholinergic neurons project to the hippocampal formation. These cholinergic projections are involved in cortical activation and memory function, particularly consolidation of short-term memory. They often appear to be damaged in patients with Alzheimer disease (AD). Drugs that enhance cholinergic function are used for improvement of memory. Other cholinergic neurons found in the brain stem tegmentum project to structures in the thalamus, brain stem, and cerebellum. The projections to the thalamus modulate arousal and the sleep-wake cycle and appear to be important in the initiation of REM sleep. Cholinergic interneurons are present in the striatum and may participate in basal ganglia control of tone, posture, and initiation of movement or selection of wanted patterns of activity. In some cases, pharmacological agents are targeted at reducing cholinergic activity in the basal ganglia in Parkinson's disease, as a complementary approach to enhancing DA activity. Acetylcholine also is used as the principal neurotransmitter in all preganglionic autonomic neurons and lower motor neurons in the spinal cord and brain stem.

#### CLINICAL POINT

Central cholinergic neurons are found in the basal forebrain (nucleus basalis of Meynert and nucleus of the diagonal band) and medial septum. The nucleus basalis cholinergic neurons are found in the substantia innominata and also along the ventral extent of the forebrain. The nucleus basalis and the nucleus of the diagonal band cholinergic neurons provide the major cholinergic input to the cerebral cortex. Cholinergic neurons of the medial septum send axons through the fornix to innervate the hippocampal formation. In patients with AD, a loss of cholinergic neurons (positive for choline acetyltransferase, the rate-limiting enzyme for acetylcholine synthesis) is most closely correlated with cognitive impairment. AD patients also show a loss of muscarinic and nicotinic cholinergic receptors and high-affinity choline uptake. Pharmacological agents such as the cholinesterase inhibitor tetrahydroaminoacridine (tacrine) have targeted cholinergic neurons in AD, and some data show a slowing in short-term memory dysfunction. Because choline is recycled for resynthesis of acetylcholine, some studies have used choline or lecithin in an attempt to boost precursor availability for added synthesis of acetylcholine; this approach has not met with great success. It may reflect the fact that AD alters many other neurotransmitter systems in the CNS in addition to the cholinergics, such as substance P, CRF, somatostatin, norepinephrine, and neuropeptide Y.





### 13.36 DISTRIBUTION OF PATHOLOGY IN THE BRAIN IN ALZHEIMER DISEASE

The characteristic pathology in the brain in Alzheimer disease (AD) is neuritic (amyloid) plaques (extracellular deposits) and neurofibrillary tangles (intracellular aggregates of hyperphosphorylated tau protein in neurons). Although these are described as the characteristic pathologic features of AD, some severely cognitively impaired individuals have normal amounts of plaques and tangles, and some individuals with extensive, autopsy-confirmed plaques and tangles were cognitively intact before death.

Neuritic plaques are usually abundant in AD, particularly in frontal and parietal cortical regions, found particularly in upper layers of the cortex. Neurofibrillary tangles are abundant in neurons in AD, starting in the medial temporal lobe

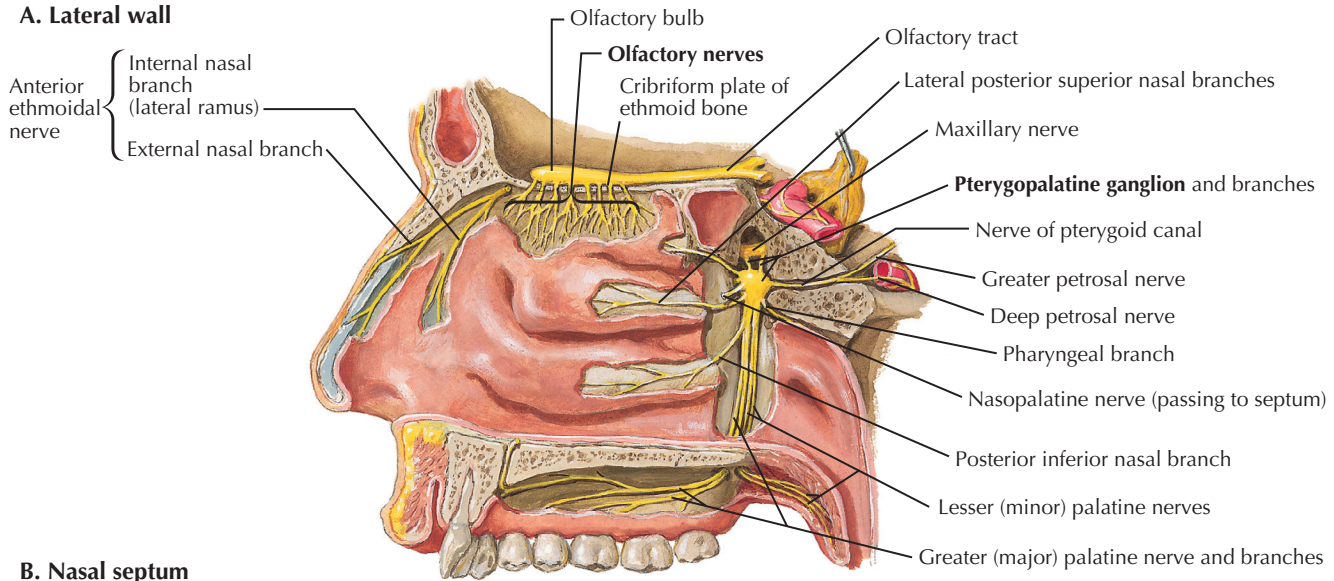
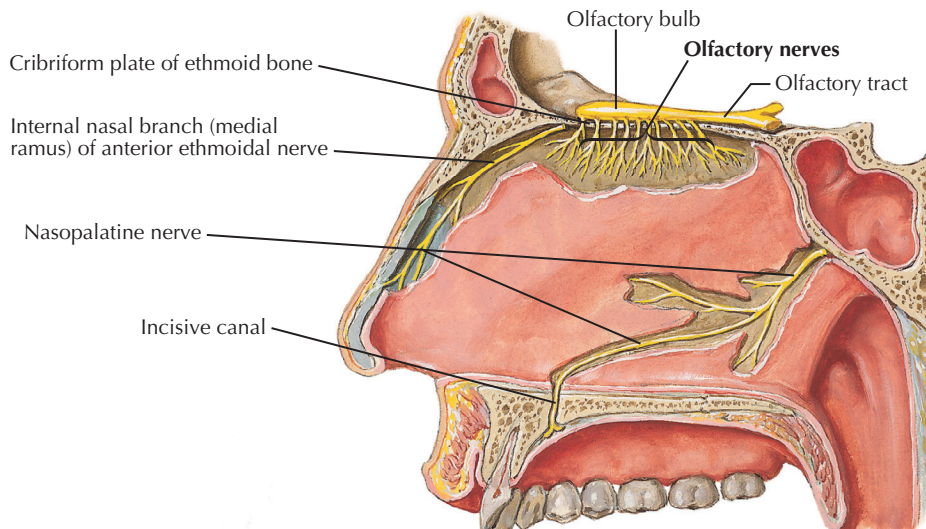
(amygdaloid region, entorhinal cortex), expanding into the hippocampal formation and cingulate cortex, and in late stages affecting widespread areas. Neurons with intracellular tangles are abundant in layer V of affected regions of cortex.

Clinical findings accompanying these pathologies include cognitive impairment, memory deficits, poor judgment and decision making, disorientation, and language impairment.

In early stages of AD, the CA1 sector of the hippocampus, the subiculum, and the entorhinal cortex are susceptible to neuronal damage from both plaques and tangles; hence, the early presence of memory deficits, especially short-term memory deficits.

Some cortical areas remain relatively spared from pathology from plaques and tangles in AD, including sensory cortices (somatosensory, auditory, visual), and motor cortex.



**A. Lateral wall****B. Nasal septum****13.37 THE OLFACTORY NERVE AND NERVES OF THE NOSE**

The olfactory nerves and their projections into the CNS are important components of forebrain function. Bipolar cells in the olfactory epithelium are the primary sensory neurons. The peripheral axon, a chemosensory transducer, and its branches respond to the unique chemical stimuli of airborne molecules entering the nose. The central axons of the bipolar neurons aggregate into groups of approximately 20 slender olfactory nerves that traverse the cribriform plate and end in glomeruli of the ipsilateral olfactory bulb. These nerves are vulnerable to tearing, which results in anosmia. Unlike neurons in other sensory systems, these bipolar neurons can proliferate and regenerate. After processing information in the olfactory bulb, mitral neurons and tufted neurons project via the olfactory tract directly and indirectly to limbic forebrain structures, including septal nuclei and amygdaloid nuclei. These projections bypass the thalamus, have immediate access to limbic forebrain structures, and directly influence the hypothalamus and its regulation of neuroendocrine and visceral/autonomic function. The olfactory system is essential for survival in many species and is involved in territorial recognition and defense, food and water acquisition, social behavior, reproductive

behavior, signaling of danger, stress responses, and other visceral functions.

**CLINICAL POINT**

The olfactory nerves possess receptors that can detect a wide range of unique odorants. This information is conveyed through the olfactory bulb to central forebrain sites, particularly those in the limbic forebrain, bypassing the thalamus, usually a processing zone for sensory projections to the forebrain. Olfaction is particularly important in recognizing the taste of food. What many people interpret as taste actually has a major olfactory component. Even very strong-tasting substances cannot be readily discerned by most people when the olfactory system is blocked, perhaps explaining the reduced gustatory experience of a good meal when someone has a cold. Clearly, both taste and smell must work together for full appreciation of food. Several regions of the brain have been identified as important sites for the interpretation of smell, including the orbitofrontal cortex and its major interconnected thalamic nucleus (medial dorsal) as well as the anterior temporal lobe. Ablation of the anterior temporal lobe, particularly on the dominant side, leads to olfactory agnosias. The involvement of the temporal lobe in the interpretation and processing of olfaction is further emphasized by olfactory auras of highly aversive or foul smells during temporal lobe seizures. Stimulation of specific olfactory receptors with odorant molecules can influence visceral responses such as appetite, relaxation, alertness, motion sickness, nausea, insomnia, headache pain, and others.



## Section III **SYSTEMIC NEUROSCIENCE**



### **14. Sensory Systems**

Somatosensory Systems

Trigeminal Sensory System

Sensory System for Taste

Auditory System

Vestibular System

Visual System

### **15. Motor Systems**

Lower Motor Neurons

Upper Motor Neurons

Cerebellum

Basal Ganglia

### **16. Autonomic-Hypothalamic-Limbic Systems**

Autonomic Nervous System

Hypothalamus and Pituitary

Limbic System

Olfactory System

# 14

## SENSORY SYSTEMS

### **Somatosensory Systems**

- 14.1** Somatosensory Afferents to the Spinal Cord
- 14.2** Spinal Somatic Reflex Actions and Pathways
- 14.3** Somatosensory System: Spinocerebellar Pathways
- 14.4** Somatosensory System: The Dorsal Column System and Epicritic Modalities
- 14.5** Somatosensory System: The Spinothalamic and Spinoreticular Systems and Protopathic Modalities
- 14.6** Spinothalamic and Spinoreticular Nociceptive Processing in the Spinal Cord
- 14.7** Mechanisms of Neuropathic Pain and Sympathetically Maintained Pain
- 14.8** Descending Control of Ascending Somatosensory Systems

### **Trigeminal Sensory System**

- 14.9** Trigeminal Sensory and Associated Sensory Systems
- 14.10** Pain-Sensitive Structures of the Head and Pain Referral

### **Sensory System for Taste**

- 14.11** Anatomy of Taste Buds and Their Receptors
- 14.12** Taste Pathways

### **Auditory System**

- 14.13** Peripheral Pathways for Sound Reception
- 14.14** Bony and Membranous Labyrinths

- 14.15** VIII Nerve Innervation of Hair Cells of the Organ of Corti
- 14.16** Cochlear Receptors
- 14.17** Afferent Auditory Pathways
- 14.18** Afferent Auditory Pathways (Continued)
- 14.19** Centrifugal (Efferent) Auditory Pathways

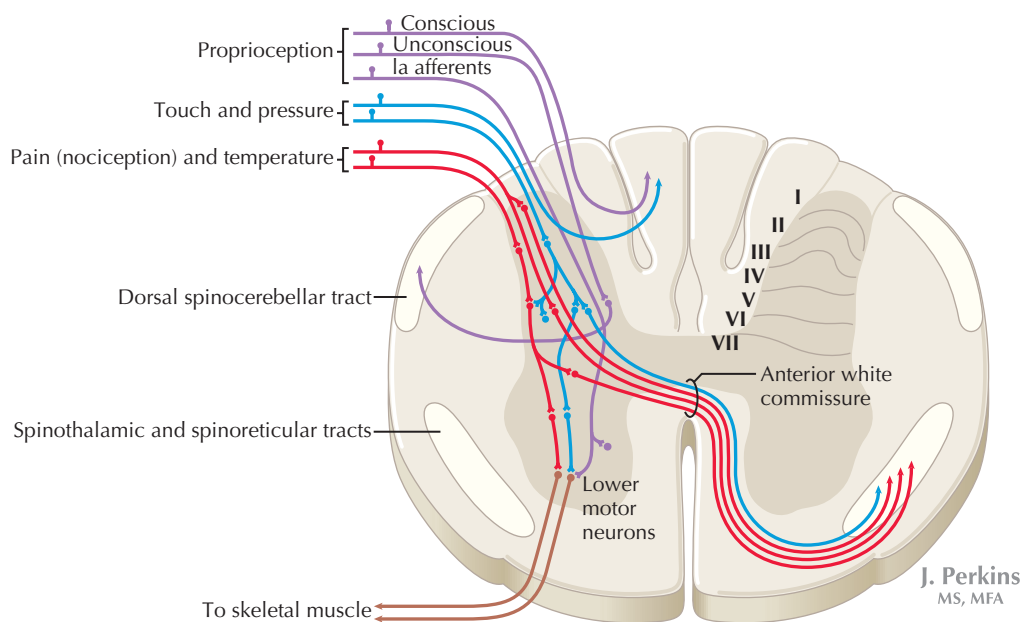
### **Vestibular System**

- 14.20** Vestibular Receptors
- 14.21** Vestibular Pathways
- 14.22** Nystagmus

### **Visual System**

- 14.23** Anatomy of the Eye
- 14.24** Anterior and Posterior Chambers of the Eye
- 14.25** The Retina: Retinal Layers
- 14.26** The Retina: Photoreceptors
- 14.27** The Retina: Optic Nerve
- 14.28** Arteries and Veins of the Eye
- 14.29** Anatomy and Relationships of the Optic Chiasm
- 14.30** Visual Pathways: Retinal Projections to the Thalamus, Hypothalamus, and Brain Stem
- 14.31** Pupillary Light Reflex
- 14.32** Visual Pathway: The Retino-Geniculo-Calcarine Pathway
- 14.33** Visual Pathways in the Parietal and Temporal Lobes
- 14.34** Visual System Lesions





## SOMATOSENSORY SYSTEMS

### 14.1 SOMATOSENSORY AFFERENTS TO THE SPINAL CORD

Unmyelinated (UNM) and small myelinated (M) axons that convey nociception and temperature sensation terminate in lamina I and V (origin of the spinothalamic tract). Other UNM axons terminate in the dorsal horn, from which neurons for polysynaptic reflexes and for the spinoreticular system originate. M axons for touch and pressure terminate in the dorsal horn, from which additional reflex connections, spinothalamic projections, and supplementary epicritic projections to the dorsal column (DC) nuclei originate. M axons also project directly into fasciculi gracilis and cuneatus, destined for nuclei gracilis and cuneatus; these lemniscal pathways process epicritic information for conscious interpretation. M proprioceptive axons (Ia afferents) terminate directly on lower motor neurons (LMNs) and on the Ia interneuronal pool. Additional M axons terminate in the dorsal horn on neurons of origin for the spinocerebellar tracts.

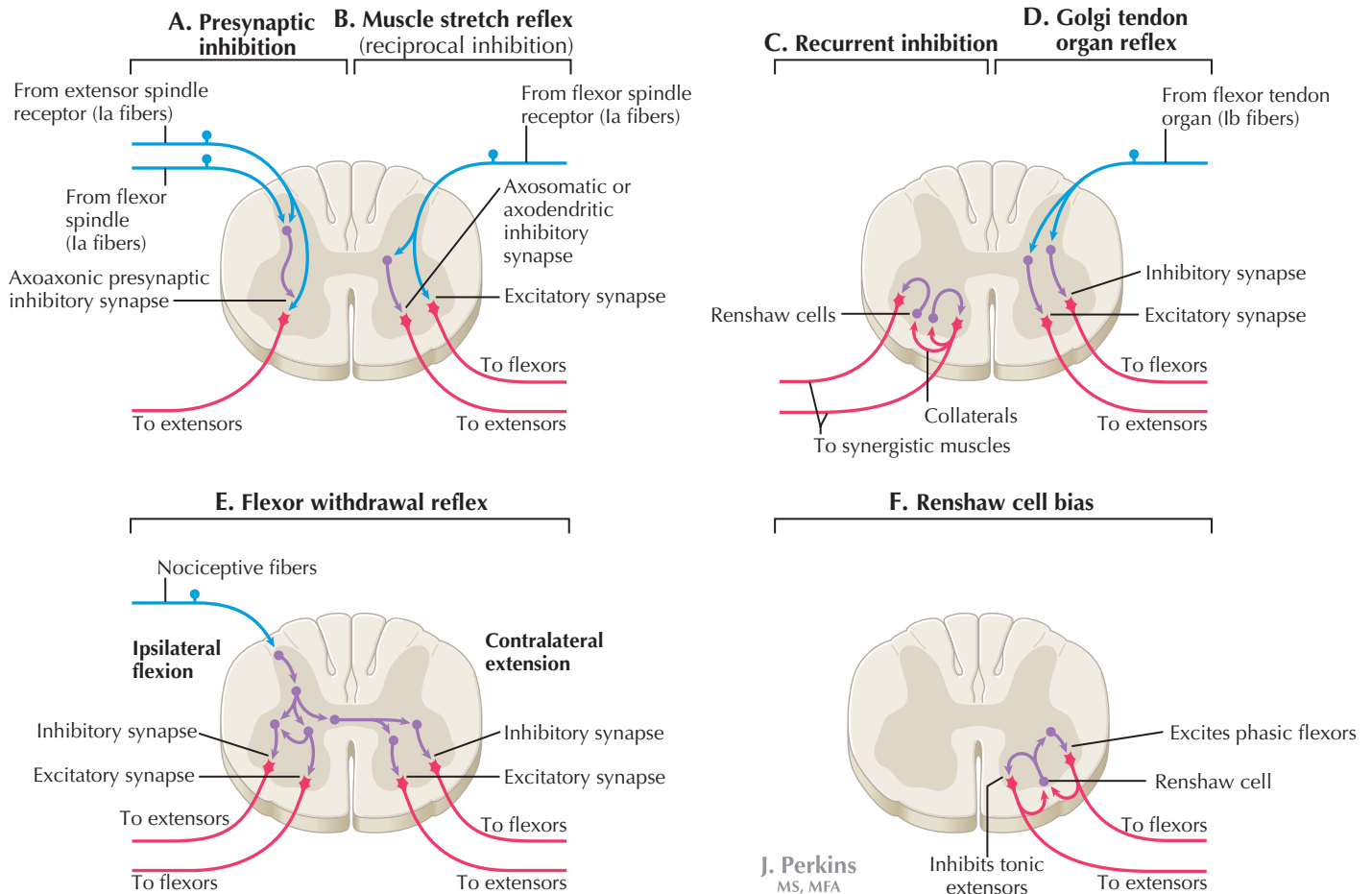
#### CLINICAL POINT

Primary afferents include both epicritic afferents (mainly larger diameter M axons that convey fine, discriminative touch, vibratory sensation, and joint position sense) and protopathic afferents (mainly small M or UNM axons that convey mainly nociceptive information and temperature sensation). These axons can be affected differentially in neuropathies. Some peripheral neuropathies can affect all modalities, leading to a total loss of sensation; other peripheral neuropathies affect selected populations of axons and their related modalities. Selective loss of protopathic modalities may occur in leprosy, in amyloid neuropathy, and in some cases of diabetic neuropathy, leading to insensitivity to pain and temperature. Selective loss of epicritic sensation may occur in some distal symmetrical polyneuropathies, neuropathy with vitamin B<sub>12</sub> deficiency, Guillain-Barré

syndrome, and others, accompanied by paresthesias (numbness and tingling, “pins and needles,” abnormal sensations), dysesthesias (disagreeable or abnormal sensations in the absence of stimulation), hyperesthesia (increased sensation with stimulation), or hypesthesia (diminished sensation with stimulation). Some neuropathic conditions also are accompanied by allodynia (pain evoked by normally nonpainful stimuli) and burning, stabbing, radiating pain. Peripheral neuropathies that affect larger diameter, M axons often can also affect the motor axons, leading to weakness and hyporeflexia or areflexia. Some small fiber neuropathies, especially diabetic neuropathies, may affect small autonomic axons to bowel, bladder, reproductive organs, and peripheral blood vessels, leading to orthostatic hypotension, bladder dysfunction, chronic gastrointestinal problems, or erectile dysfunction.

#### CLINICAL POINT

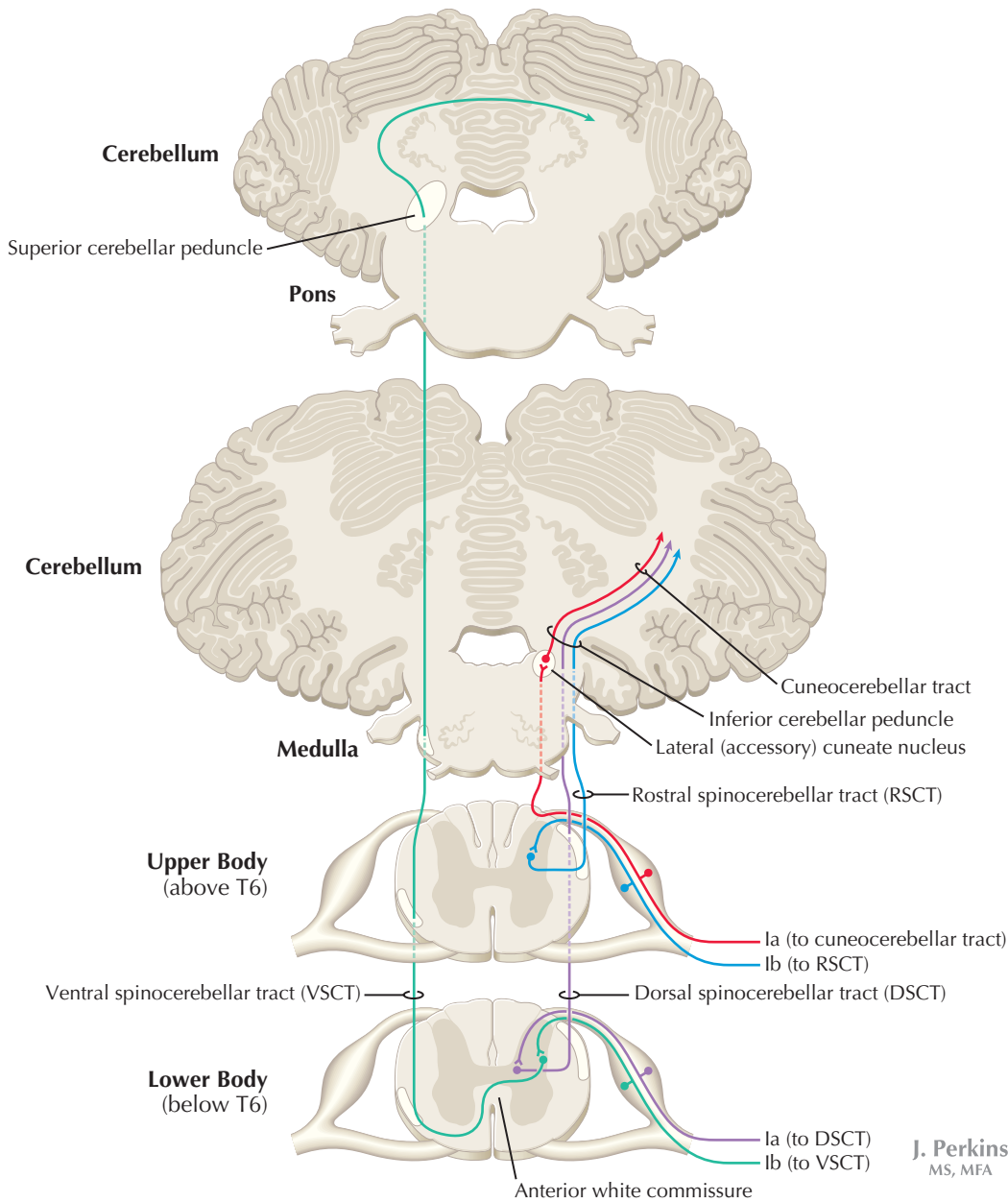
The monosynaptic reflex (the muscle stretch reflex) is tested in a clinical neurological examination. Specific muscle tendons are tapped, with the expected result of contraction of the homonymous muscle (e.g., tapping of the patellar tendon resulting in contraction of the ipsilateral quadriceps muscle). The muscle stretch reflexes routinely tested in a neurological examination include the biceps reflex, triceps reflex, brachioradialis reflex, patellar (knee-jerk) reflex, and the ankle-jerk reflex on both sides. The reflexes are graded on a numerical scale ranging from hyporeflexic to normoreflexic to hyperreflexic; normal physiological reflexes may vary in responsiveness, so the result of reflex testing must be considered in conjunction with other clinical signs and symptoms. For example, hyperreflexia in a pathological state such as stroke or spinal cord injury may be accompanied by hypertonia of the affected muscle, spasticity, abnormal reflexes (extensor plantar response), and repetitive alternating hyperreflexic responses (clonus). In contrast, hyporeflexia or areflexia accompanying peripheral neuropathy may be accompanied by muscle weakness and flaccidity and diminished sensation of epicritic modalities, protopathic modalities, or both. More formal testing of reflexic responses can be done with electromyography and conduction velocity studies.



## 14.2 SPINAL SOMATIC REFLEX ACTIONS AND PATHWAYS

**A, Presynaptic inhibition.** Some interneurons synapse on the terminal arborizations of other axons, as in the case of some afferent pools associated with muscle stretch reflexes. These axoaxonic contacts permit the modulation of neurotransmitter release from the second (target) axon terminal by depolarization of the terminal membrane, altering the influx of  $\text{Ca}^{++}$ . **B, Muscle stretch reflex.** In the muscle stretch reflex, Ia afferents excite the homonymous LMN pool directly and inhibit the antagonist LMN pool reciprocally via Ia inhibitory interneurons. **C, Recurrent inhibition.** Some interneurons receive recurrent collaterals from axons (e.g., LMN axons) and project back onto the dendrites or cell body of origin of that axon, usually inhibiting that neuron. This process can help to regulate the excitability and timing of excitation of the target neurons. Collaterals of LMN axons excite Renshaw cells (large interneurons), which inhibit the LMN of origin as well as LMNs projecting to synergistic muscles. Renshaw inhibition permits wiping the slate clean, after original excitation, of pools of LMNs, requiring additional incoming stimulation in order to excite these LMNs again. **D, Golgi tendon organ reflex.** Ib axons from Golgi tendon organs in muscle tendons terminate on pools of interneurons that inhibit LMNs to the homonymous muscle disynaptically and excite LMNs to the antagonist muscle reciprocally. The action of this reflex as a

protective mechanism to prevent damage to a muscle during generation of maximal tension on the tendon is seen in attempted passive stretch of a spastic muscle; the resultant inhibition of the homonymous LMN pool is called a clasp-knife reflex. **E, Flexor withdrawal reflex.** A flexor reflex (also called a withdrawal reflex or a nociceptive reflex) occurs when afferents derived from a noxious stimulus terminate on pools of interneurons that excite appropriate pools of LMNs (often flexor LMNs) to bring about a protective withdrawal from the source of the noxious stimulus. These interneurons also inhibit the antagonist LMNs through reciprocal inhibition. Flexor reflexes can extend throughout the spinal cord, as happens when one touches a hot stove with a finger; the result is the removal of the entire arm, or even the entire body, away from the source of heat. These flexor reflexes may involve both sides of spinal cord. **F, Renshaw cell bias.** Some reflex responses such as Renshaw reflexes (see part C) may result in the distribution of influence (bias) in a manner that favors a particular type of action. Renshaw cells receive inputs from axon collaterals of both flexor and extensor LMNs, but their projections are directed mainly toward the inhibition of tonic extensor LMNs (and through reciprocal inhibition with the excitation of phasic flexor LMNs). Thus, the Renshaw cell response favors flexor movements and helps to inhibit extensor movements.



J. Perkins  
MS, MFA

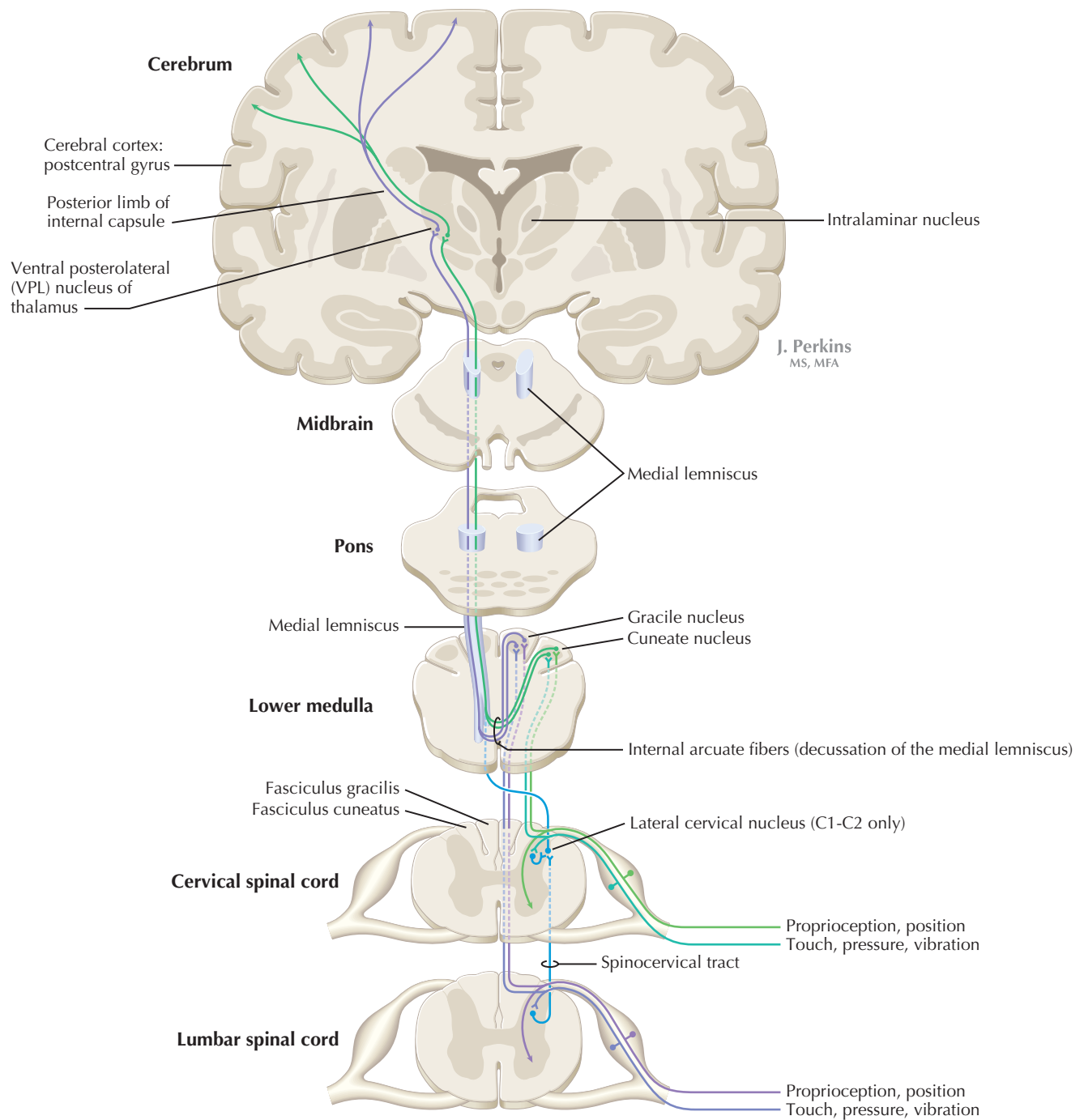
### 14.3 SOMATOSENSORY SYSTEM: SPINOCEREBELLAR PATHWAYS

Proprioceptive primary somatosensory axons from joints, tendons, and ligaments (represented in this figure by Ib afferents from Golgi tendon organs) terminate on neurons of origin (border cells, dorsal horn) of the ventral spinocerebellar tract (VSCT) and the rostral spinocerebellar tract (RSCT) from the lower and upper body, respectively (level T6 is the cut-off point). Proprioceptive primary somatosensory axons from muscle spindles (represented in this figure by Ia afferents) terminate on neurons of origin (Clarke's nucleus, lateral {external} cuneate nucleus of the medulla) of the dorsal spinocerebellar tract (DSCT) and the cuneocerebellar tract from the lower and upper body, respectively (level T6 is the cut-off point). The DSCT, RSCT, and cuneocerebellar tracts remain ipsilateral. The VSCT crosses twice, once in the anterior white commissure of the spinal cord and again in the cerebellum.

#### CLINICAL POINT

The dorsal and ventral spinocerebellar pathways travel in a conspicuous site at the lateral edge of the lateral funiculus throughout most of its length; these pathways are vulnerable to lesions that impinge on this zone of the spinal cord. They include tumors, radiculopathies with accompanying myelopathies, combined-system degeneration, demyelinating diseases, vascular infarcts in the anterior circulation of the cord, Brown-Séquard lesions, and other pathologies. Such a lesion, if superficial in the lateral funiculus, results in ipsilateral ataxia, dysmetria, clumsiness, and mild hypotonia, with impaired ability to perform heel-to-shin testing and tandem walking. However, lesions of the lateral funiculus often also involve the descending upper motor axons of the lateral corticospinal tract and the rubrospinal tract. Lesions that involve these tracts cause ipsilateral spastic hemiparesis or monoparesis below the level of the lesion, depending on the level of the lesion. The resulting spastic weakness, hyperreflexia, and hyper-tonus predominate in the clinical picture, thus masking the spinocerebellar symptomatology. Thus, an initial picture of spinocerebellar damage may give way to a progressive picture of spastic paresis on the same side.

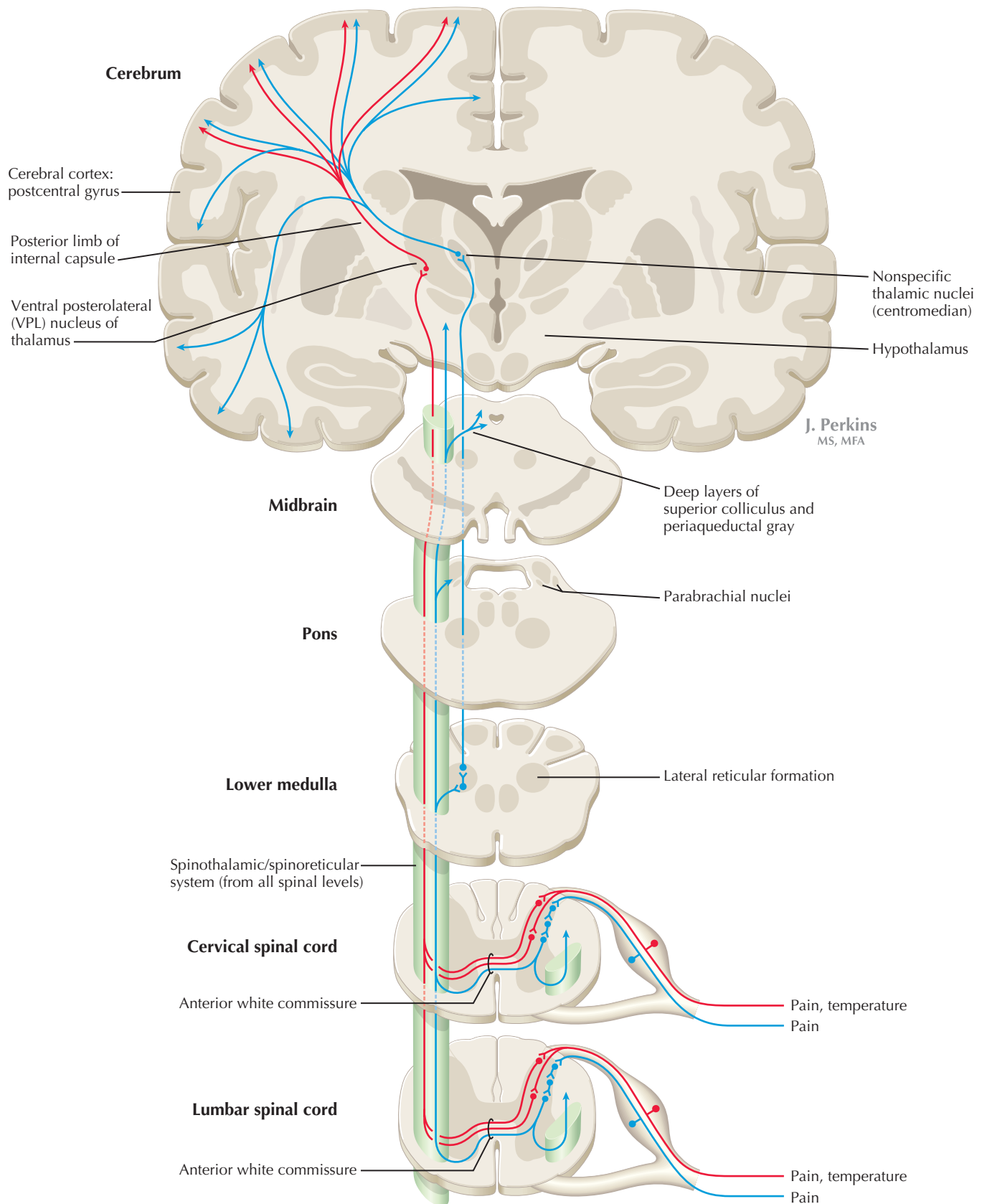




#### 14.4 SOMATOSENSORY SYSTEM: THE DORSAL COLUMN SYSTEM AND EPICRITIC MODALITIES

Primary somatosensory myelinated axons conveying fine, discriminative touch, pressure, vibratory sensation, and consciousness of joint position project directly into the DC system (fasciculus gracilis for lower body, below T6, and fasciculus cuneatus for upper body, T6 and above), where they are topographically organized. They terminate in nuclei gracilis and cuneatus, respectively, from which the medial lemniscus originates. This tract crosses (decussates) in the medulla, rostral to the decussation of the pyramids, and projects to the ventroposterolateral (VPL) nucleus of the thalamus. Axons of neurons in the VPL nucleus terminate in the primary sensory cortex topographically. The entire DC/medial lemniscal

system is topographically organized; the lower body is represented medially in the primary somatosensory cortex, and the upper body (and face from trigeminal projections) is represented laterally. This representation is sometimes drawn proportionally (the resultant figure is called a homunculus); information from the fingers and hands has far greater representation in the cerebral cortex than information from the back. The spinocervical system is a small supplement to the DC system. Primary afferent projections terminate in the medial part of the dorsal horn; these neurons project to the lateral cervical nucleus (in C1 and C2 only). This nucleus contributes additional crossed axons with polysynaptic mechanoreceptive information. The supplemental epicritic information contributing to the dorsal column/medial lemniscal system ascends in the dorsal portion of the lateral funiculus.



**Somatosensory System: The Spinothalamic and Spinoreticular Systems and Protopathic Modalities**

#### 14.5 SOMATOSENSORY SYSTEM: THE SPINOTHALAMIC AND SPINORETICULAR SYSTEMS AND PROTOPATHIC MODALITIES (CONTINUED)

Primary somatosensory unmyelinated (C fibers) and small myelinated (A delta fibers) that convey nociceptive information (fast, localizing pain), temperature sensation, and light, moving touch terminate on neurons in lamina I and V. These dorsal horn neurons send crossed axons into the spinothalamic tract, projecting to neurons in the VPL nucleus of the thalamus (*red*). This pool of neurons in the VPL nucleus is different from the pool receiving input from nuclei gracilis and cuneatus from the DC system. These thalamic neurons in the VPL nucleus project to the second somatosensory cortex (SII) as well as to the primary sensory cortex. Primary sensory C fibers also terminate in the dorsal horn and contribute to a large, cascading network for bilateral projections into the spinoreticular tract (*blue*). This system ends mainly in the reticular formation, from which polysynaptic projections lead to nonspecific, medial dorsal, and anterior thalamic nuclei. Some spinoreticular fibers also terminate in the deeper layers of the superior colliculus (spinotectal pathway), in the parabrachial nuclei of the pons, and in the periaqueductal gray. Cortical regions such as the cingulate, insular, and prefrontal regions then process and interpret nociceptive information related to slow, agonizing, excruciating pain. In addition, axonal projections from neurons in the dorsal horn of the spinal cord, descending nucleus of V, and parabrachial nuclei of the pons terminate directly in the hypothalamus. These nociceptive axons to the hypothalamus help to coordinate visceral responses (e.g., fight-or-flight, autonomic reactions to pain such as blood pressure and cardiovascular responses, stress hormone secretion of cortisol and epinephrine, and emotional responses). Direct somatosensory inputs also help to mediate sexual responses and oxytocin release for milk let-down from suckling.

##### CLINICAL POINT

The spinothalamic tract conveys lemniscal information from primary afferents for nociception and temperature sensation to secondary sensory neurons in lamina I and V of the dorsal horn of the spinal cord. These dorsal horn neurons then project contralateral spinothalamic tract axons to the VPL nucleus of the thalamus, which in turn sends some information about “fast pain” (not outlasting the duration of the stimulus) to sensory cortices I and II in the parietal lobe. This

is the principal protopathic system tested in the neurological examination, using light pin prick and touching the body with test tubes containing water of various temperatures. This spinothalamic tract system does not convey chronic, agonizing, deep pain that characterizes many chronic diseases; such chronic “slow” pain is conveyed through a vast polysynaptic network through the dorsal horn of the spinal cord and then the lateral reticular formation of the brain. This spinoreticular processed information eventually reaches the nonspecific thalamic nuclei (such as the centromedian) and is conveyed to limbic structures for more subjective, interpretative aspects of pain and to the hypothalamus for appropriate visceral autonomic and hormonal responses to pain. This latter spinoreticular network can be influenced by a host of other inputs, including the cortex, the limbic system, the descending forebrain and diencephalic systems, and collaterals of the DC system. Collaterals of the DC system can gate nociceptive processing through the dorsal horn by activating neurons that dampen transmission of information through the cascading dorsal horn network. This process is evoked in a simple fashion by light rubbing on or adjacent to an injured part of the body. In a more chronic fashion, DC stimulation (by a transcutaneous electrical nerve stimulation [TENS] unit) can electrically activate large-diameter axons which then gate the painful stimuli bombarding the dorsal horn nociceptive axons.

##### CLINICAL POINT

The DC system consists of fasciculus gracilis (lower half of the body, with T6 cutoff) and fasciculus cuneatus (upper half of the body). These pathways consist of primary sensory axons conveying fine, discriminative touch sensation, vibratory sensation, and joint-position sense (the epicritic sensations) toward the first synapse in the secondary sensory nuclei gracilis and cuneatus in the caudal medulla. These epicritic sensations are called primary DC modalities, the basic information coded mainly by large-diameter myelinated axons. Additional DC modalities are sometimes tested if the primary modalities are intact, including two-point discrimination, stereognosis (knowing what an object is just by touch), and graphesthesia (interpreting a number drawn into the palm of the hand). These are considered cortical modalities of the DC system; they require that the primary DC modalities be intact and also require the ability of the sensory cortices to interpret the information conveyed and to draw conclusions about that information. If the primary modalities are impaired, there is no reason to attempt to test the cortical modalities that depend on unimpaired primary modalities. Pure lesions of the DC system do not entirely eliminate the primary epicritic modalities, they just remove some interpretive capabilities; such a patient may realize that a vibratory stimulus is being applied to the upper extremity but may be unable to distinguish vibratory stimuli of different frequencies. The dorsal portion of the lateral funiculus carries additional epicritic information to the DC nuclei from the spinal cord dorsal horn. A lesion of both the DC and the dorsal portion of the lateral funiculus results in total loss of epicritic sensation on the affected side.



## Gating Mechanism

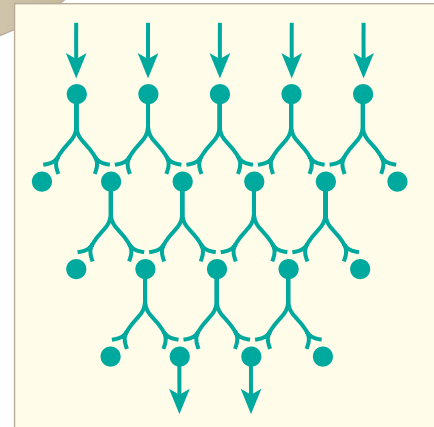
Dorsal column afferent  
Nociceptive afferent

## Spinal Mechanisms of Nociceptive Processing

C and A delta  
C and A delta  
C

J. Perkins  
MS, MFA

Spinothalamic/  
spinoreticular  
tract

Recruitment by  
Convergence

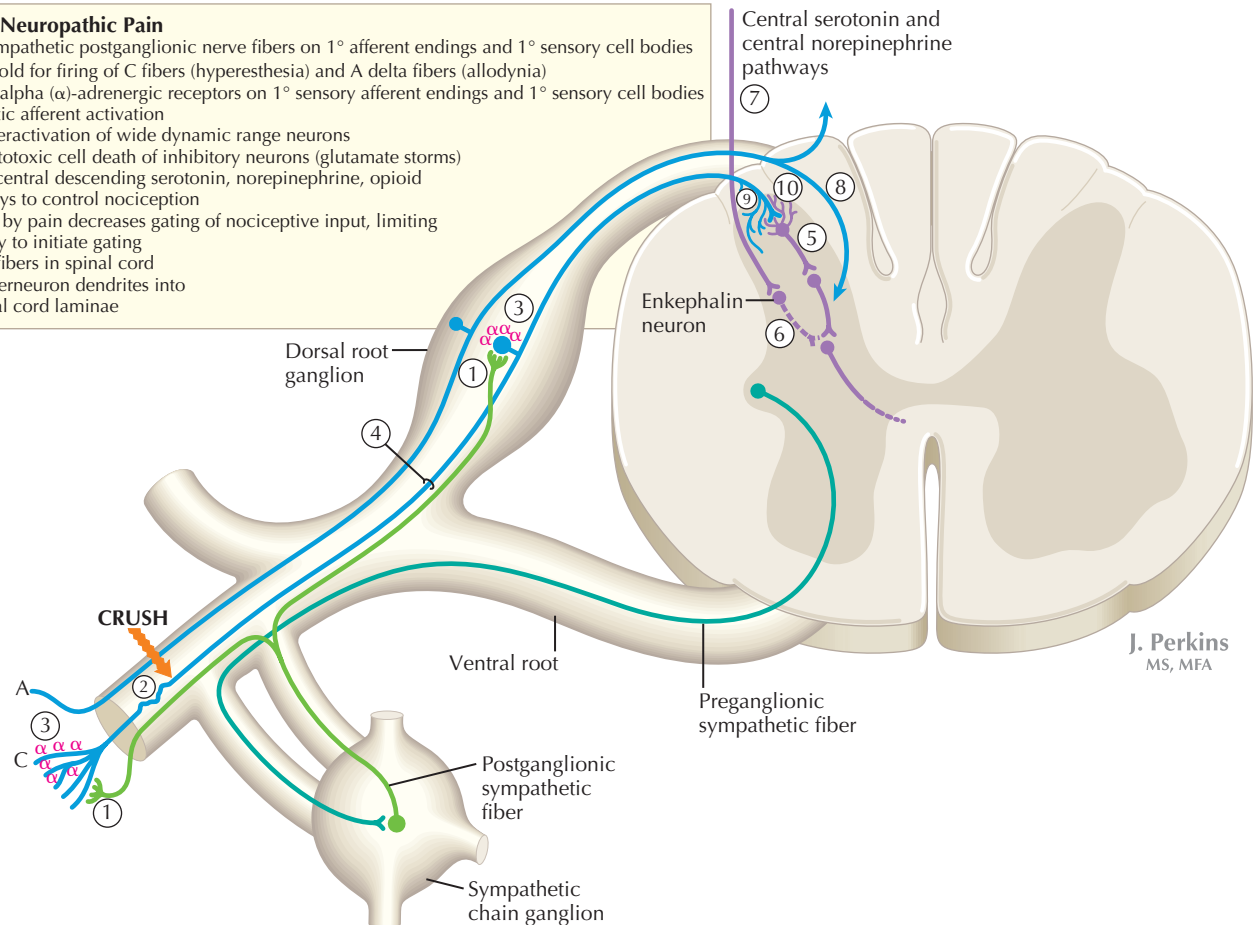
#### 14.6 SPINOTHALAMIC AND SPINORETICULAR NOCEPTIVE PROCESSING IN THE SPINAL CORD

Primary afferents (C and A delta fibers) conveying fast, localized pain and temperature sensation terminate in laminae I and V of the dorsal horn of the spinal cord, from which the crossed spinothalamic axons originate. Unmyelinated primary afferents (C fibers) also terminate on neurons in the dorsal horn, from which a cascading system involving recruitment, convergence, and polysynaptic interconnections originates. This system (shown in red) contributes to the spinoreticular

tract (mainly crossed, but some are uncrossed), which projects into the RF and continues polysynaptically to nonspecific, medial dorsal and anterior thalamic nuclei. This system contributes to perception of excruciating pain and its emotional connotation via cortical regions such as the cingulate, insular, and prefrontal cortices. The gating mechanism, shown in blue on the left, allows primary DC axon collaterals to dampen pain processing in the dorsal horn via inhibitory interneuronal connections that inhibit the flow of information through the cascading dorsal horn system that contributes to the spinoreticular pathway.

**Mechanisms of Neuropathic Pain**

1. Sprouting of sympathetic postganglionic nerve fibers on 1° afferent endings and 1° sensory cell bodies
2. Lowered threshold for firing of C fibers (hyperesthesia) and A delta fibers (allodynia)
3. Proliferation of alpha ( $\alpha$ )-adrenergic receptors on 1° sensory afferent endings and 1° sensory cell bodies
4. Possible ephaptic afferent activation
5. Permanent hyperactivation of wide dynamic range neurons
6. Glutamate excitotoxic cell death of inhibitory neurons (glutamate storms)
7. Inadequacy of central descending serotonin, norepinephrine, opioid peptide pathways to control nociception
8. Immobilization by pain decreases gating of nociceptive input, limiting physical therapy to initiate gating
9. Sprouting of C fibers in spinal cord
10. Extension of interneuron dendrites into additional spinal cord laminae



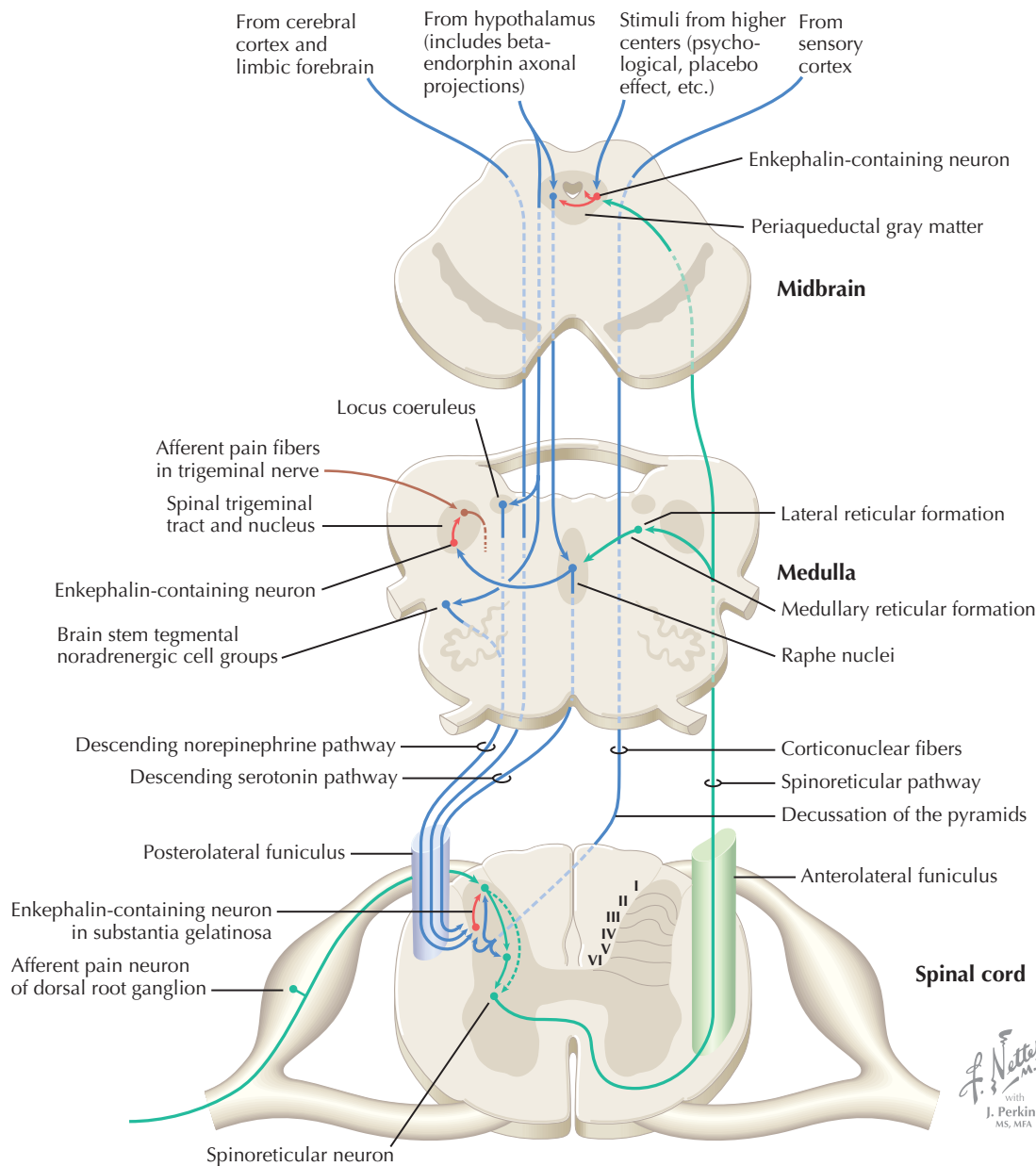
J. Perkins  
MS, MFA

### 14.7 MECHANISMS OF NEUROPATHIC PAIN AND SYMPATHETICALLY MAINTAINED PAIN

The cascading dorsal horn system receives primary afferent C fibers of nociceptive origin and projects into the spinoreticular system for the conscious interpretation of excruciating pain and neuropathic pain, shown in this illustration. Connections from the sympathetic nervous system can innervate terminals and cell bodies of primary nociceptive neurons directly. In neuropathic pain syndromes such as complex regional pain syndrome (CRPS), formerly called reflex sympathetic dystrophy (RSD), sympathetic postganglionic neurons may activate receptors on greatly sensitized primary afferent nerve terminals and cell bodies, either directly (via synapses) or indirectly (through secretion of norepinephrine into the blood); such activation may exacerbate the perception of the neuropathic pain. Multiple mechanisms are thought to contribute to sensitization of pain-related neurons and presence of chronic, agonizing neuropathic pain in CRPS and related syndromes. These mechanisms are noted in this illustration as numbered sites. Descending central noradrenergic and serotonergic projections are thought to play an important modulatory role in the processing of neuropathic and non-neuropathic pain.

#### CLINICAL POINT

In some cases of nerve damage or compression, particularly that associated with a sprain, a crush injury, a direct injection into a nerve, or even relatively minor trauma, a pathological reaction of primary afferents can result in a chronic, neuropathic pain syndrome called reflex sympathetic dystrophy, more recently renamed CRPS. It is related to the type of chronic, agonizing central pain experienced in phantom limb syndrome. CRPS affects the hand, arm, and shoulder to a greater extent than the lower extremity. Intense burning or stabbing pain is felt, with allodynia and hyperesthesia (extreme sensitivity to touch and painful stimuli, respectively). When this phenomenon affects one nerve (perhaps following a bullet wound) it is sometimes called causalgia. The primary afferents involved in CRPS appear to proliferate alpha-adrenergic receptors on their sensory receptor endings and on the dorsal root ganglion cell body and often show extraordinary sensitivity to catecholamines, which provoke a lower threshold for response to nociceptive stimuli. In syndromes such as CRPS, permanent destruction of dorsal horn inhibitory interneurons (by glutamate excitotoxicity) and permanently altered thresholds for wide dynamic-range spinoreticular neurons also have been observed. Sympathetic-related characteristics may be noted in CRPS, such as changes in skin appearance due to vascular flow changes (vasomotor), atrophic skin and nails (trophic changes), altered sweating and skin temperature (sudomotor), and altered bone density on a tri-phasic bone scan. Treatment must occur quickly after detection and must employ simultaneous vigorous therapeutic approaches. Treatment choices normally include analgesics, tricyclic or other antidepressants to alter pain threshold in the spinal cord, membrane-stabilizing agents (e.g., Neurontin), physical therapy, and nerve stimulation of large diameter myelinated "gating" axons.



#### 14.8 DESCENDING CONTROL OF ASCENDING SOMATOSENSORY SYSTEMS

The processing of nociceptive information in the dorsal horn of the spinal cord can be modulated by descending connections from the cerebral cortex; limbic forebrain structures; the hypothalamus (paraventricular nucleus); the periaqueductal gray; the RF of the brain stem; the central noradrenergic neurons (of locus coeruleus and other brain stem tegmental groups); and the serotonergic (5HT) neurons (nucleus raphe magnus). The central descending noradrenergic and 5HT pathways, modulated by the periaqueductal gray, and other higher centers, are particularly important for endogenous and exogenous (i.e., opioid) modulation of pain.

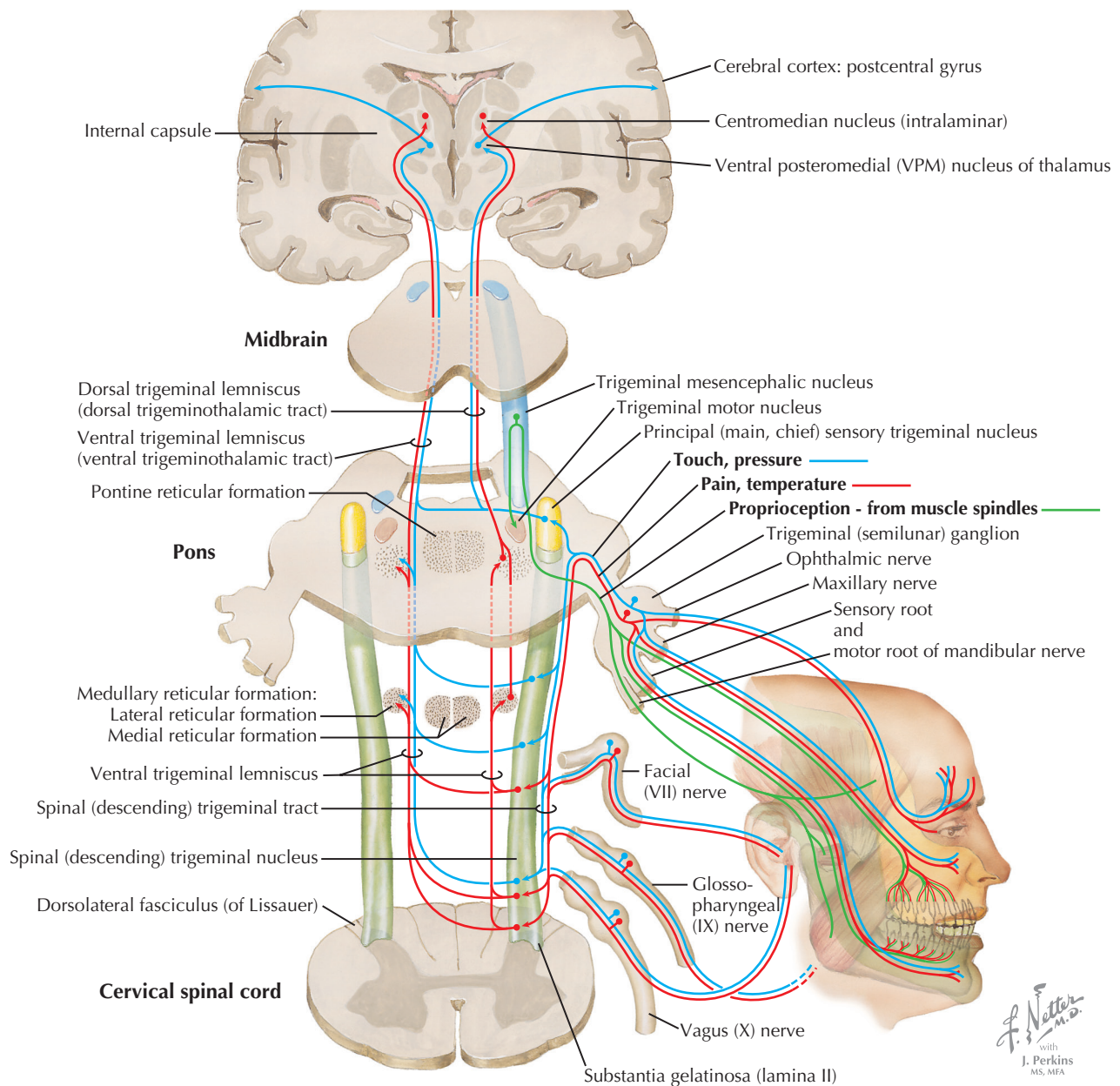
##### CLINICAL POINT

Several regions of the central nervous system (CNS) send projections, direct and indirect, to regulate nociceptive processing through the

dorsal horn of the spinal cord for the body and the descending nucleus of V for the face. These areas include regions of cerebral cortex, limbic forebrain areas, hypothalamic regions including endorphin nuclei, and sensory cortical centrifugal connections. Some of these projections use endogenous opiates. Enkephalin and dynorphin interneurons are found in pain-processing regions, particularly in the dorsal horn of the spinal cord and the descending nucleus of V, and in many hypothalamic and limbic sites that may be involved in the subjective interpretation of pain. The beta-endorphin neurons of the periaqueductal region of the hypothalamus send connections to the periaqueductal gray, locus coeruleus and brain stem noradrenergic nuclei, the raphe nuclei, and many limbic regions. The periaqueductal gray is particularly important for opioid activation of the nucleus raphe magnus and other descending monoamine pathways that activate enkephalins and assist in opiate analgesia. The periaqueductal gray–raphe connection is essential for full functionality of opioid analgesia. Systemic administration of synthetic opiates activates neurons of the periaqueductal region of the hypothalamus and periaqueductal gray, resulting in analgesia.

*F. Netter M.D.*  
with  
J. Perkins  
MS, MFA





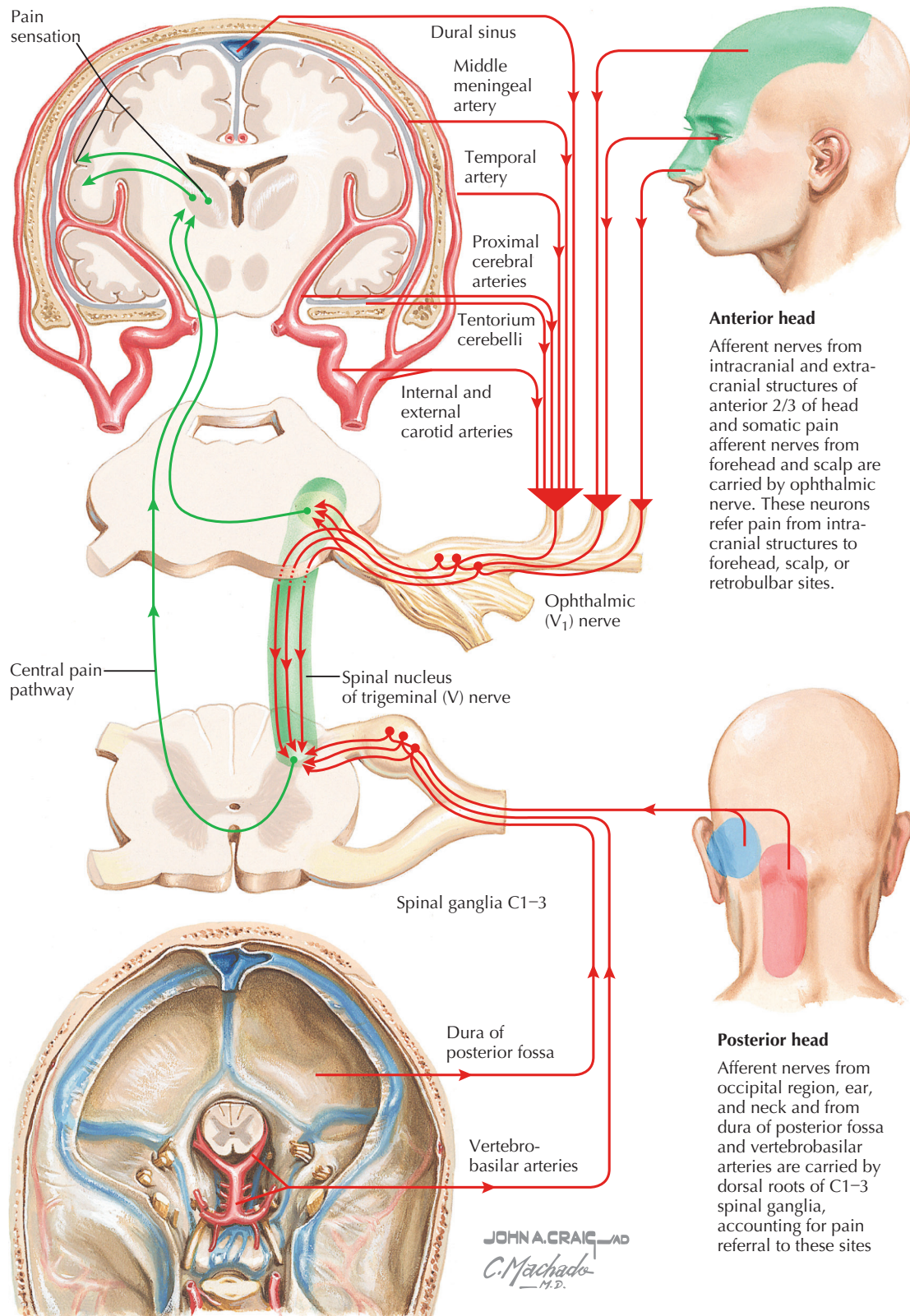
*F. Netter M.D.*  
with  
J. Perkins  
MS, MFA

## TRIGEMINAL SENSORY SYSTEM

### 14.9 TRIGEMINAL SENSORY AND ASSOCIATED SENSORY SYSTEMS

Axons of primary ( $1^{\circ}$ ) sensory trigeminal neurons enter the brain stem, travel in the descending (spinal) tract of V, and terminate in the descending (spinal) nucleus of V. Axons of the trigeminal ganglion (V) supply the face, anterior oral cavity, and teeth and gums; axons of the geniculate ganglion (VII) and jugular ganglion (X) supply a small zone of the external ear. Axons of the petrosal ganglion (IX) supply general sensation to the posterior oral cavity and pharynx. Axons of the descending nucleus of V project into the ventral trigeminal lemniscus (ventral trigeminothalamic tract) (mainly crossed axons) and terminate in the ventral posteromedial (VPM) nucleus of the thalamus. The VPM nucleus projects to the lateral primary sensory cortex and to intralaminar thalamic nuclei, which are associated with nociceptive processing. The

caudal descending nucleus also sends contralateral projections to the RF for processing of excruciating pain (similar to the spinoreticular system). Primary sensory axons carrying fine, discriminative modalities from V (similar to the DC system) terminate in the rostral portion of the descending nucleus of V and in the main (chief) sensory nucleus of V, which contribute to the ventral trigeminothalamic tract. A portion of the main sensory nucleus also projects ipsilaterally to the VPM nucleus via the dorsal trigeminothalamic tract. Although most of the trigeminal system is represented on the lateral portion of the contralateral primary sensory cortex (postcentral gyrus), part of the epicritic trigeminal projections as well as taste are represented in the ipsilateral sensory cortex. The mesencephalic nucleus of V is the only primary sensory nucleus found inside the CNS; these neurons supply muscle spindles for masticatory and extraocular muscles and mediate associated muscle spindle reflexes. See page 420 for a Clinical Point.

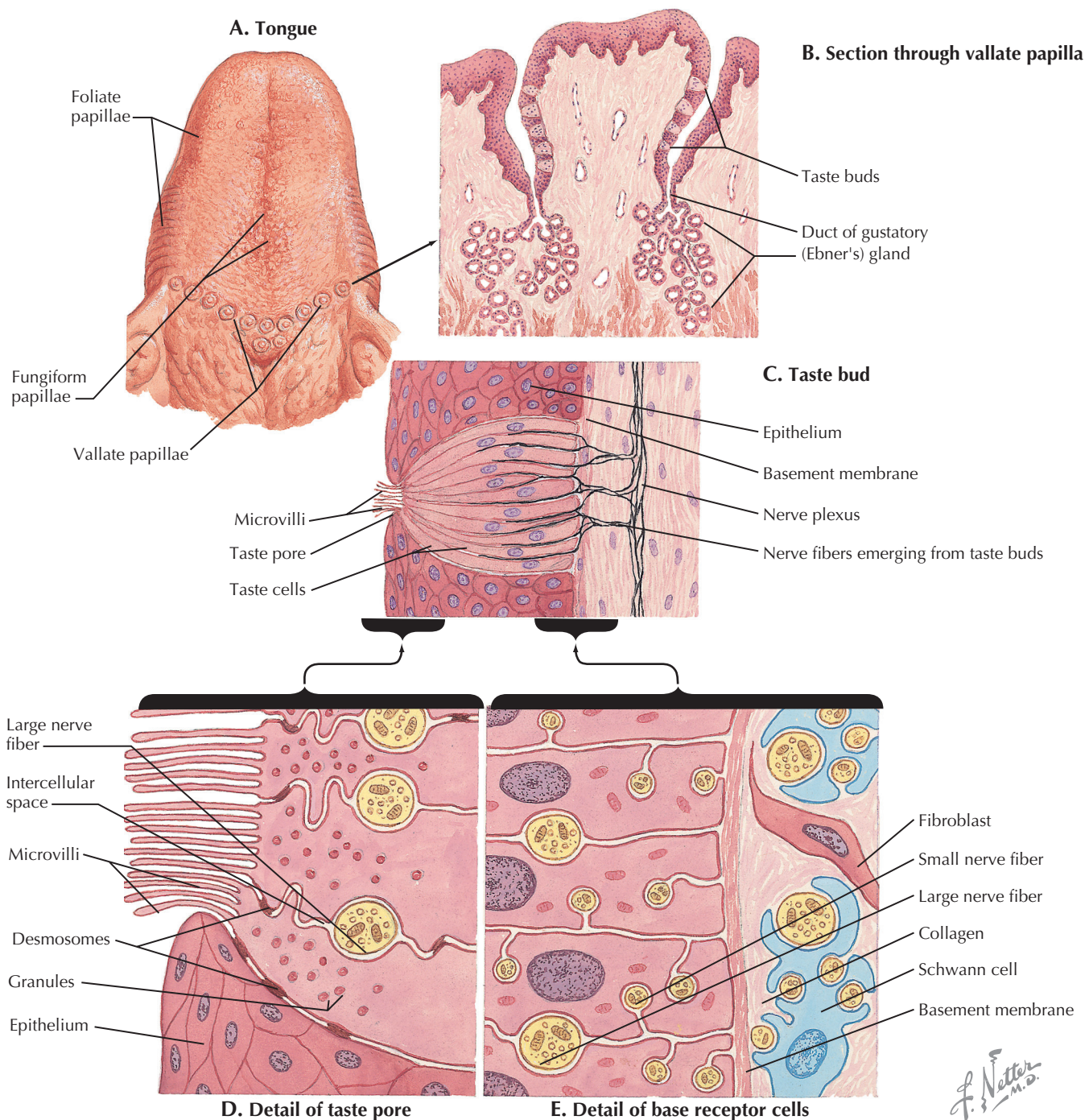


#### 14.10 PAIN-SENSITIVE STRUCTURES OF THE HEAD AND PAIN REFERRAL

Pain-sensitive structures of the head include dural structures (e.g., sinuses, tentorium cerebelli), arteries, and muscles.

Primary headaches can arise as migraine headaches, tension headaches, and neuralgias. Secondary headaches can arise from tumors, abscesses, hematomas, bleeding (e.g., ruptured berry aneurysm), and meningitis or meningeal irritation.





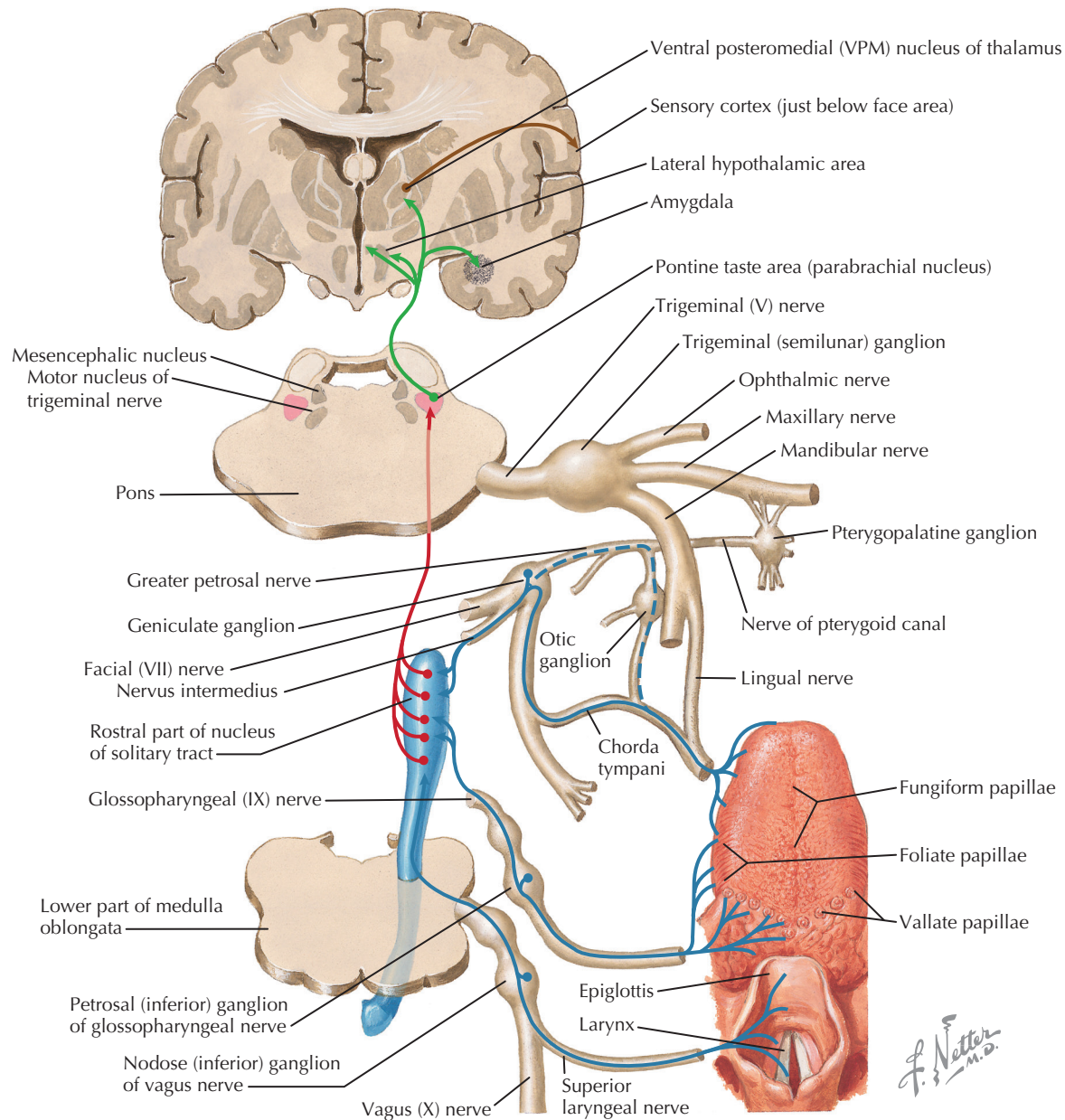
## SENSORY SYSTEM FOR TASTE

### 14.11 ANATOMY OF TASTE BUDS AND THEIR RECEPTORS

Taste buds are chemosensory transducers that consist of bundles of columnar cells that lie within the epithelium. They translate individual molecular configurations or combinations of molecules for salty, sweet, sour, and bitter sensations

into action potentials of both large and small primary sensory axons. The taste buds are found on the anterior and posterior regions of the tongue and, less frequently, on the palate and epiglottis, mainly in children. Nerve fibers for taste show complex responses of electrical activity across populations of many nerve fibers. The integrative interpretation of taste takes place in the CNS.





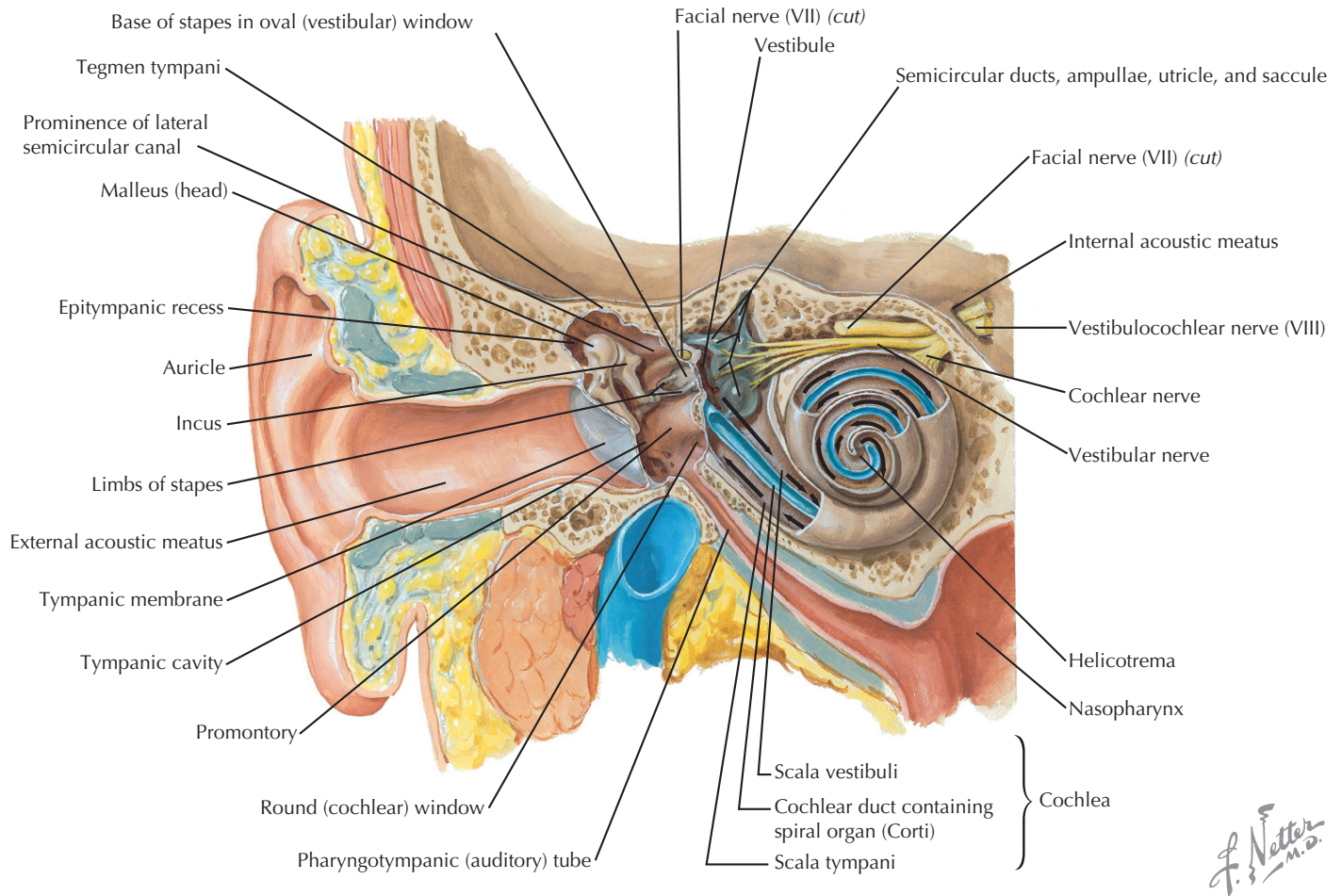
### 14.12 TASTE PATHWAYS

Primary sensory axons of neurons of the geniculate ganglion (VII), petrosal ganglion (IX), and nodose (inferior) ganglion (X), supply taste buds on the anterior two thirds of the tongue, the posterior one third of the tongue, and the epiglottis and palate, respectively. These axons terminate in the rostral part of nucleus solitarius (nucleus of the solitary tract), which sends ipsilateral projections mainly to the parabrachial nucleus in the pons (and a few projections to nucleus VPM of the thalamus). The parabrachial nucleus projects fibers to nucleus VPM of the thalamus, to the hypothalamus (lateral hypothalamic area, paraventricular nucleus), and to amygdaloid nuclei. These nonthalamic projections are associated with the emotional, motivational, and behavioral aspects of taste and food intake.

#### CLINICAL POINT

Taste pathways arise from primary receptors, the taste buds, which are associated with cranial nerves VII (anterior two thirds), IX (posterior

one third), and X (epiglottis). The taste buds detect sweet, salty, bitter, and sour tastes; each taste bud appears to be associated mainly with one such modality. Combined taste receptor activation can code for a tremendous array of subtle tastes and flavors. Olfaction plays a major role in the discrimination of what an individual perceives to be taste. The primary taste afferents terminate in the rostral nucleus solitarius, which projects mainly to a pontine parabrachial nucleus and then to the parvocellular part of the VPM nucleus of the thalamus, several hypothalamic sites, and the amygdaloid complex. Some cortical areas, such as the anterior portion of the insular cortex and a lateral zone of the posterior orbitofrontal cortex, are involved in subjective aspects of taste and the gustatory experience. These pathways are mainly ipsilateral. Chemical influences can also have a profound effect on taste. Smoking may blunt taste. Many illnesses, including severe nasal congestion, liver dysfunction, autonomic problems, postradiation responses, some vitamin deficiencies, and some medications, may distort or alter the tastes of foods or may leave a lingering, unpleasant, distinctive taste. Many chemotherapeutic agents also profoundly alter taste sensation, perhaps accounting in part for loss of appetite in such individuals.

**Frontal section**

*J. Netter M.D.*

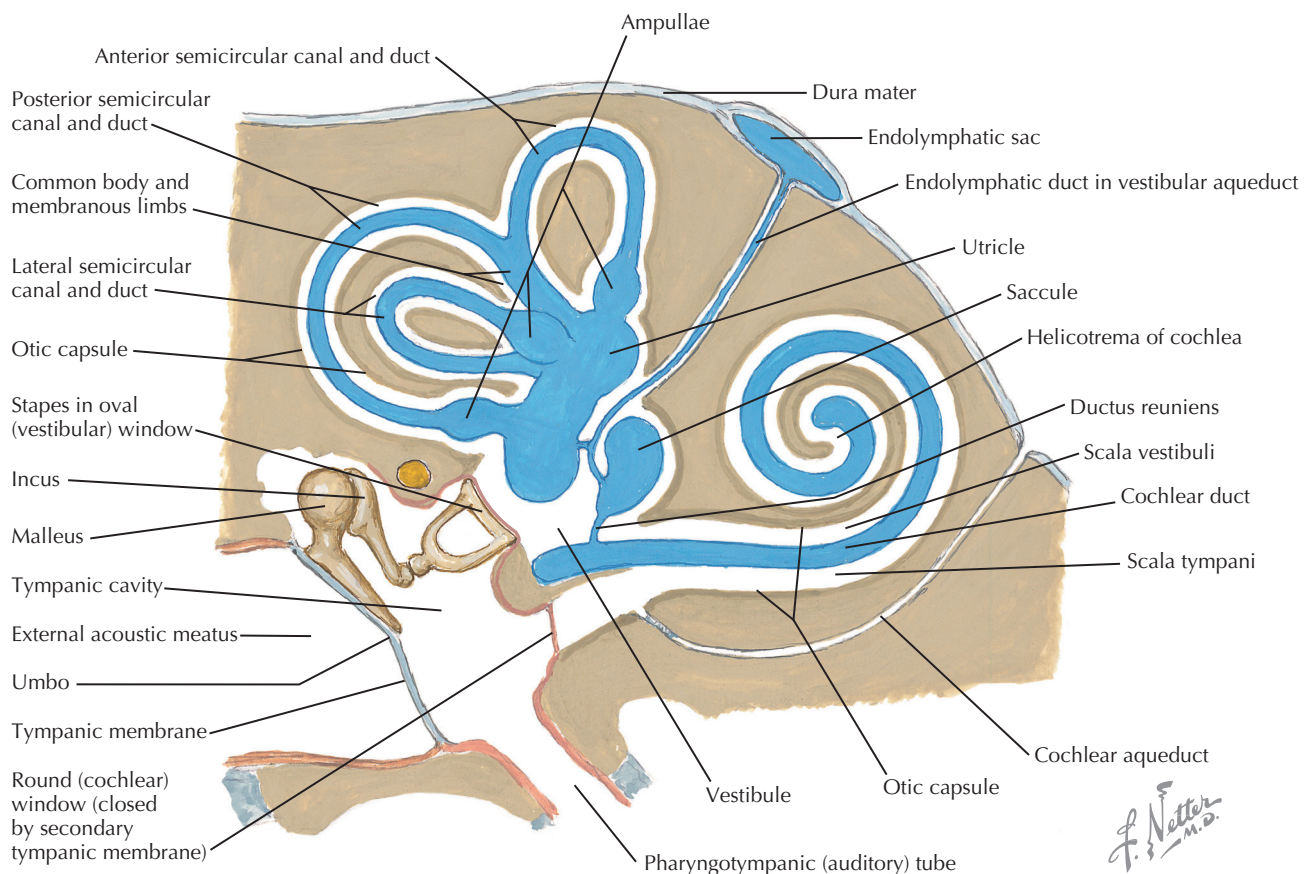
**AUDITORY SYSTEM****14.13 PERIPHERAL PATHWAYS FOR SOUND RECEPTION**

The sound transduction process involves complex mechanical transduction of sound waves through the external ear and the external acoustic meatus and across the tympanic membrane; there it is leveraged as a mechanical force by the bones of the middle ear (ossicles) via the oval window to produce a fluid wave in the cochlear duct. This fluid wave causes differential movement of the basilar membrane, stimulating hairs on the apical portion of hair cells to release neurotransmitters that stimulate primary sensory axons of neurons of the cochlear (spiral) ganglion. The basilar membrane in the cochlea shows maximal displacement spatially according to the frequency of impinging tones, with low frequencies maximally stimulating the apex (helicotrema) and high frequencies maximally stimulating the base. The eustachian (pharyngotympanic) tube permits pressure equilibrium between the middle ear and the outside world.

**CLINICAL POINT**

Hearing loss may be partial or total and can involve virtually any range of detectable frequencies. The most devastating for human communication is a loss in the frequencies of speech (300 to 3000 Hz) of 40 or more decibels. In general, hearing loss can be subdivided into two categories: sensorineural and conductive. Sensorineural hearing loss involves damage to the hair cells, the auditory nerve, or central auditory pathways. Because of the neural damage, both air conduction and bone conduction are diminished. Conductive hearing loss involves damage to the outer or middle ear. Air conduction is impaired because the sound is not properly transduced into the inner ear, but bone conduction is normal. These two types of hearing loss can be tested for at the bedside by using a tuning fork of 512 Hz. The Weber test involves placing the vibrating tuning fork on the center of the forehead. Normally, the patient hears the fork equally in both ears. With sensorineural loss, the sound is heard best in the unaffected ear; with conductive loss, the sound is heard best in the affected ear. The Rinne test involves holding the vibrating tuning fork against the mastoid bone. When the fork is no longer heard, it is immediately placed just outside the external auditory meatus. Normally, air conduction is more effective than bone conduction, and the fork will again be heard when moved adjacent to the external auditory meatus (air conducting sound better than bone). If conductive hearing loss is present, once bone conduction is no longer heard, air conduction also will not be heard (bone conducting sound better than air). If sensorineural hearing loss is present, air conduction may be greater than bone conduction, although both may be diminished.



**Bony and membranous labyrinths****14.14 BONY AND MEMBRANOUS LABYRINTHS**

The relationship between the cochlea and the vestibular apparatus (utricle, saccule, semicircular canals, and ducts) and the bony labyrinth that surrounds them is illustrated. The ossicles (malleus, incus, stapes) leverage the movement of the tympanic membrane to produce movement of the oval window. Movement of the oval window causes a fluid wave to move through the scala vestibuli and the scala tympani of the cochlea and ricochet onto the round window, causing differential movement of the basilar membrane and stimulation of selected responsive hair cells. The three semicircular canals are located at 90-degree angles to each other, representing tilted X, Y, and Z axes.

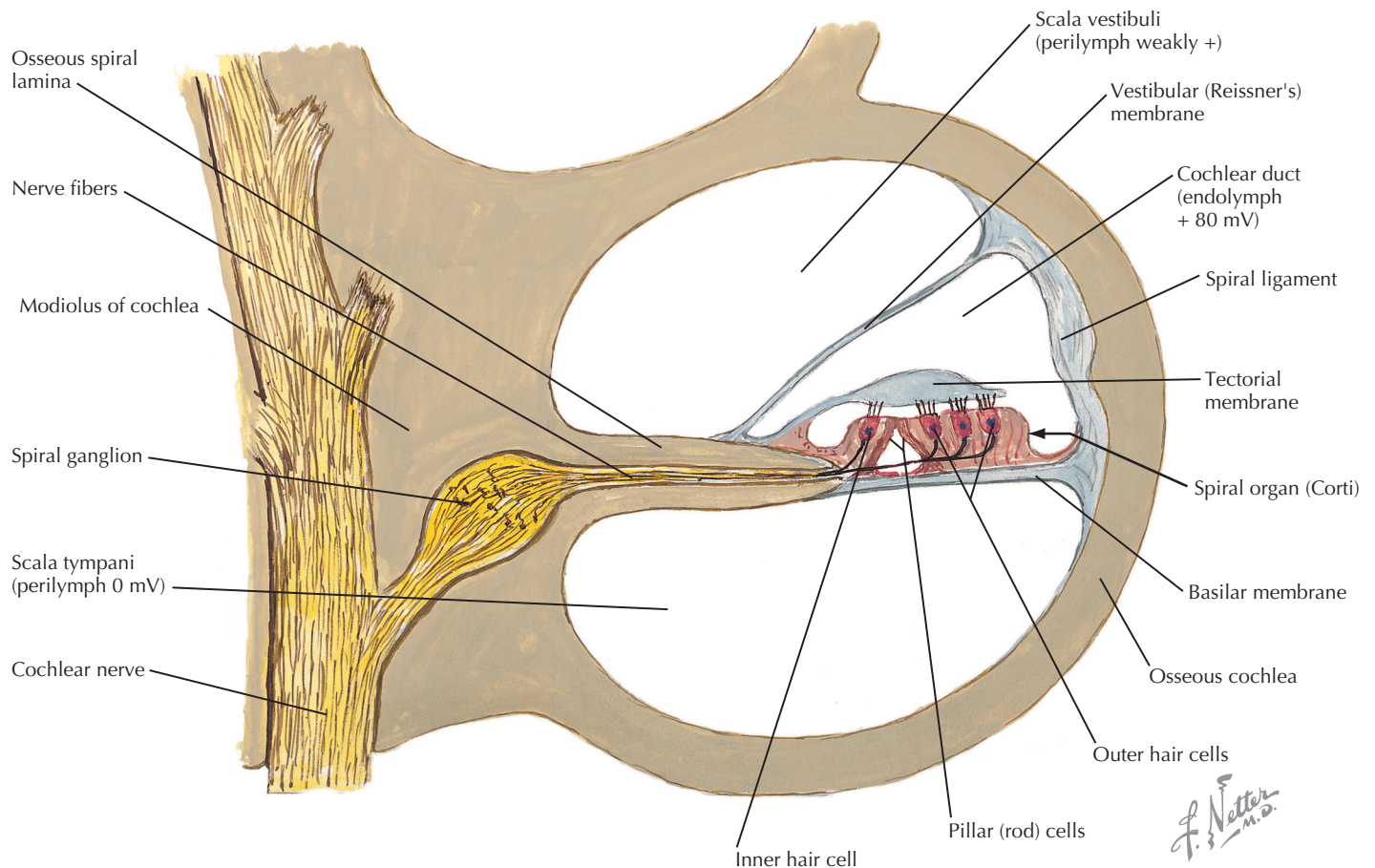
**CLINICAL POINT**

The semicircular canals (ducts) contain the ampullae that have hair cells that respond to angular acceleration. The utricle contains the otolith organ in the macula that responds to linear acceleration and detects gravitation. The saccule responds best to low-frequency vibratory stimuli. The cochlea contains the hair cells that respond to fluid movements in the scalae vestibuli and tympani, brought about by the leveraging of the ossicles against the oval window; this movement affects hair cells in the cochlear duct.

The activity of the utricle can sometimes become distorted when debris moves away from the hairs and induces activation of the hair cells in the ampulla of the posterior semicircular canal. This produces vertigo and nystagmus that are associated with a specific position of the head (benign postural or positional vertigo). This disorder is the most common cause of vertigo seen in neurological practice. These attacks commonly occur when the patient is lying down, moving to a particular position, or tilting the head back; they may recur either briefly or for a longer period of days or weeks. Attacks can be induced by an examiner through the Hallpike maneuver (tilting the patient's head back and then 30 degrees to the side), resulting in a brief attack of vertigo and nystagmus. No pharmacological treatment is available. Attempts to reposition the debris by deliberate Hallpike-like head movements have met with some success.



## Section through turn of cochlea

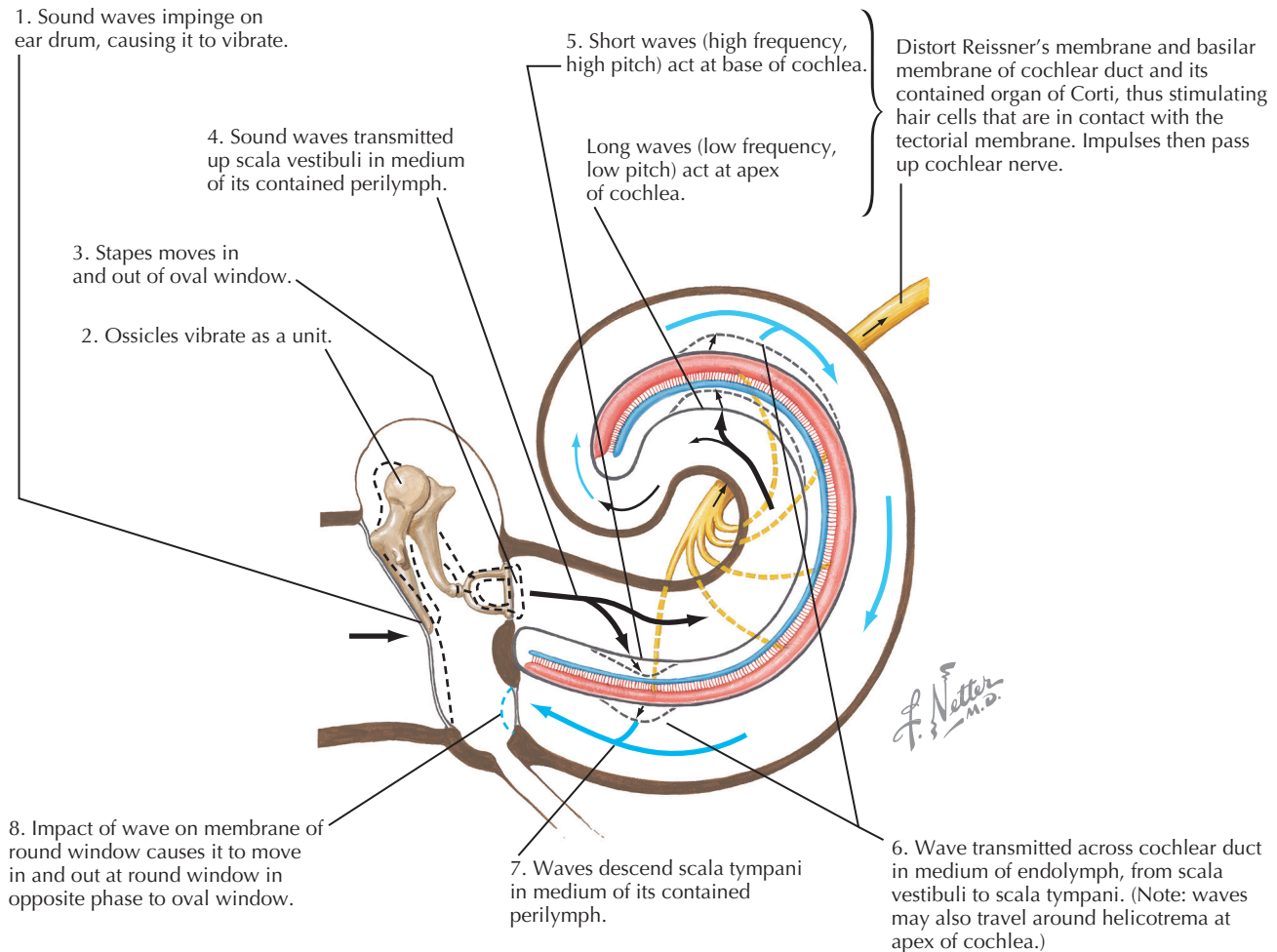


### 14.15 VIII NERVE INNERVATION OF HAIR CELLS OF THE ORGAN OF CORTI

Primary sensory axons of the spiral (cochlear) ganglion innervate inner and outer hair cells of the organ of Corti, located on the basilar membrane. The axons are activated by release of neurotransmitters from the hair cells, which occurs when the hairs on the apical surface are moved by shearing forces resulting from movement of the basilar membrane (fluid wave through the scalae vestibuli and tympani) in relation to the more rigidly fixed tectorial membrane. This represents the complex transduction process of the conversion of external sound waves to action potentials in spiral ganglion axons. The ionic potentials (in mV) are indicated for the scala tympani and vestibuli (perilymph) and the cochlear duct (endolymph). These potential differences contribute to the excitability of the hair cells.

#### CLINICAL POINT

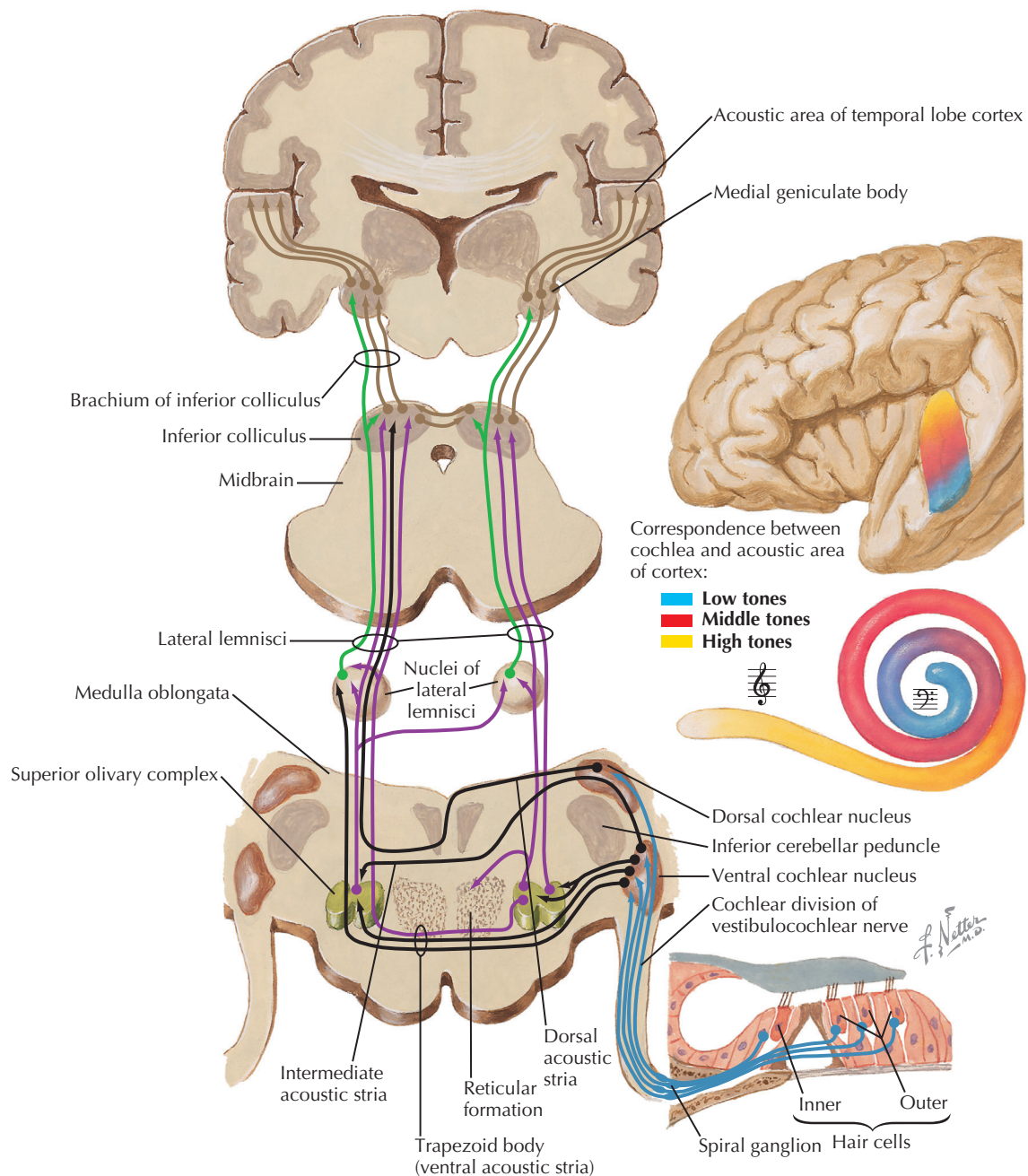
Hair cells in the organ of Corti respond to fluid movements in the scalae vestibuli and tympani that induce shearing motion of the tectorial membrane relative to the basilar membrane. Each region of the spiraled cochlea contains hair cells that respond optimally to movement of the basilar membrane; low frequencies stimulate hair cell movement in the apex (helicotrema), and high frequencies stimulate hair cell movement in the basilar coils of the cochlea. The hair cells can be damaged by many pathological processes, such as viral infections (e.g., mumps); drugs (e.g., quinine); antibiotics; exposure to sustained loud noise; and age-related deterioration caused by free-radical damage. Exposure to loud noises above 85 decibels can selectively damage hair cells, especially those in the basilar coils of the cochlea that transduce high-frequency sounds. High-pitched machinery noise (jet engines), gunfire without ear protection, exposure to loud music at concerts or by earphones, and loud ambient noise in construction or industrial sites can induce temporary damage that can become permanent with repeated exposure. Environmental protection regulations now require ear protection in personnel working at such sites.



### 14.16 COCHLEAR RECEPTORS

Fluid movement through scala vestibuli, around the helicotrema, and back through the scala tympani differentially moves the basilar membrane on which the organ of Corti and its hair cells reside. Movement of hairs on the apical portion of the hair cells by shearing forces of the tectorial membrane

results in their depolarization and the release of neurotransmitters. This release stimulates action potentials in the primary afferent axons of spiral ganglion cells. Efferent axons from the olivocochlear bundle, controlled by descending central auditory pathways, can modulate the excitability of hair cells and the sensory transduction process.



### 14.17 AFFERENT AUDITORY PATHWAYS

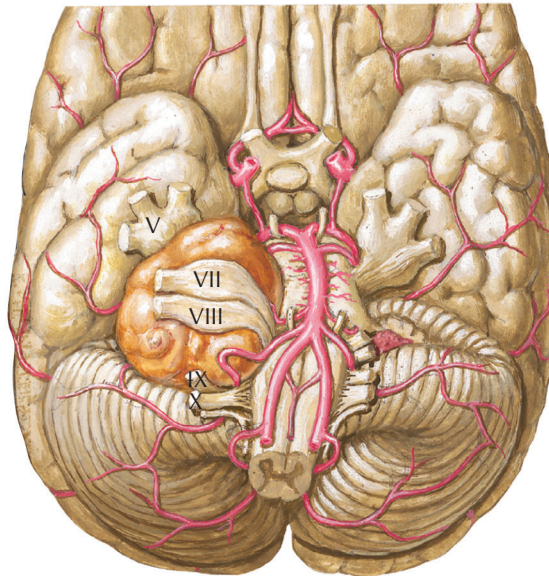
Central axon projections of the spiral ganglion neurons terminate in dorsal and ventral cochlear nuclei in several tonotopic maps (receptor origination shown in the cochlea in colors). These cochlear nuclei project into the lateral lemniscus via acoustic striae; many of these projections remain ipsilateral. The lateral lemniscus terminates in the nucleus of the inferior colliculus, which in turn projects via the brachium of the inferior colliculus to the medial geniculate body (nucleus) of the thalamus. The thalamus sends tonotopical projections to the primary auditory cortex on the transverse gyrus of

Heschl. Several accessory auditory brain stem nuclei (the superior olivary nucleus for lateral sound localization, the nuclei of the trapezoid body [not shown], and the lateral lemniscus) send both crossed and uncrossed projections through the lateral lemniscus. Sound is represented throughout the afferent auditory pathways bilaterally; thus a unilateral lesion in the lateral lemniscus, auditory thalamus, auditory radiations, or auditory cortex does not produce contralateral deafness. With such a lesion, there is a diminution in hearing and auditory neglect contralateral to the lesion with bilateral simultaneous stimulation.

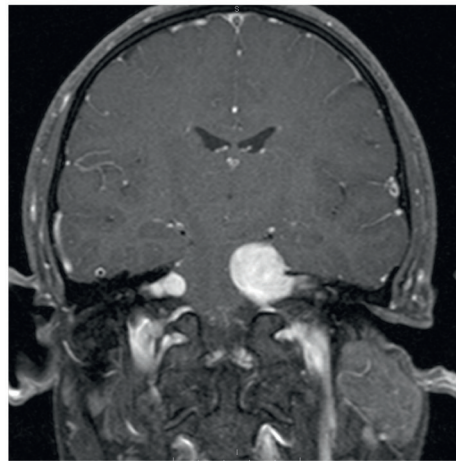
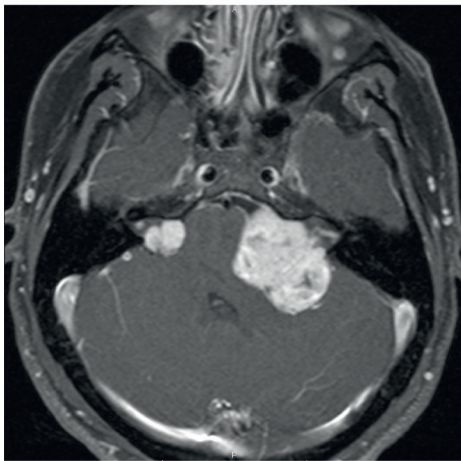


Large acoustic Schwannoma intruding in the cerebellopontine angle, causing damage to both the vestibular and cochlear portions of CN VIII, CN VII, other cranial nerves (V, IX, X), and brain stem structures

*F. Netter M.D.*



MRI of vestibular schwannoma at the cerebellopontine angle; axial (left) and coronal (right)

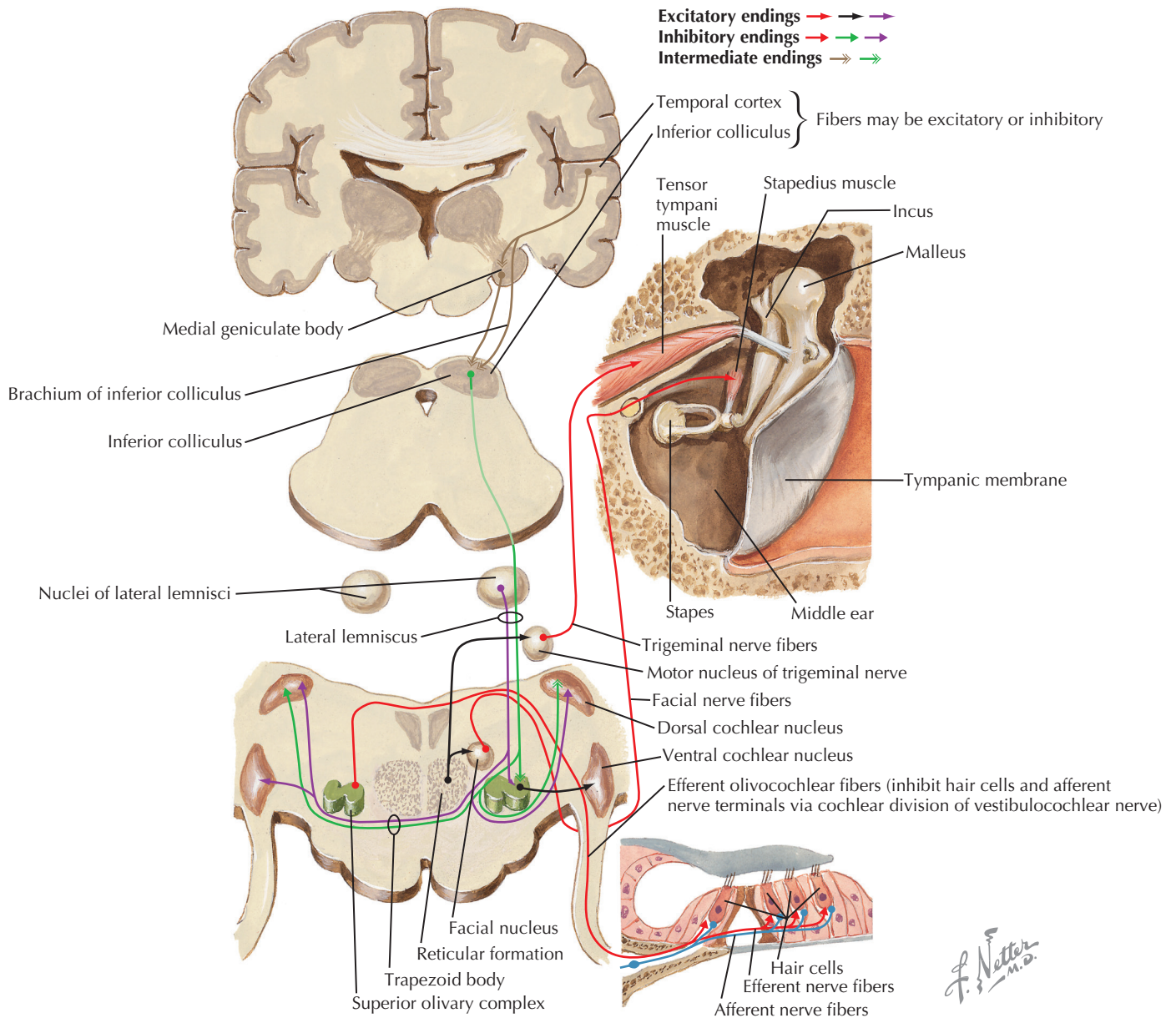


## 14.18 AFFERENT AUDITORY PATHWAYS (CONTINUED)

### CLINICAL POINT

The cochlear nerve contains axons that innervate the hair cells of the organ of Corti in the spirals of the cochlea. Primary cochlear axons enter the lateral portion of the caudal pons, terminating in the dorsal and ventral cochlear nuclei with several tonotopically representative maps of the auditory frequency world. The auditory nerve can be damaged by infections, tumors (e.g., acoustic Schwannoma), and traumas, particularly those associated with the petrous portion of the temporal bone. Irritation of auditory nerve fibers can produce tinnitus, a sense of ringing in the ears (or buzzing, humming, clicking,

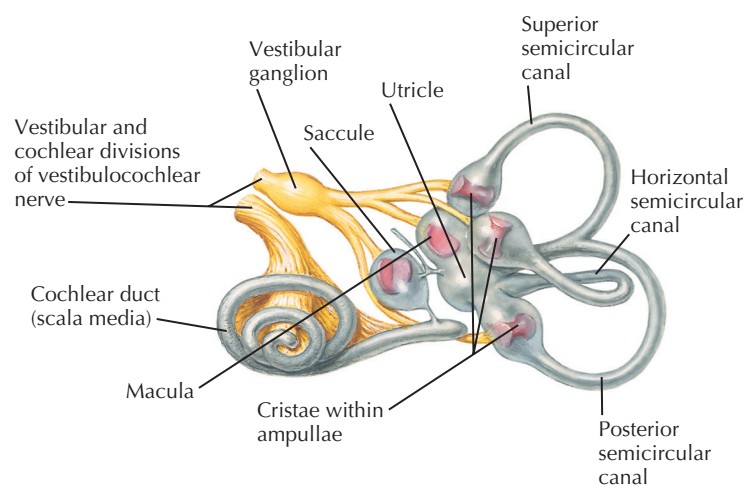
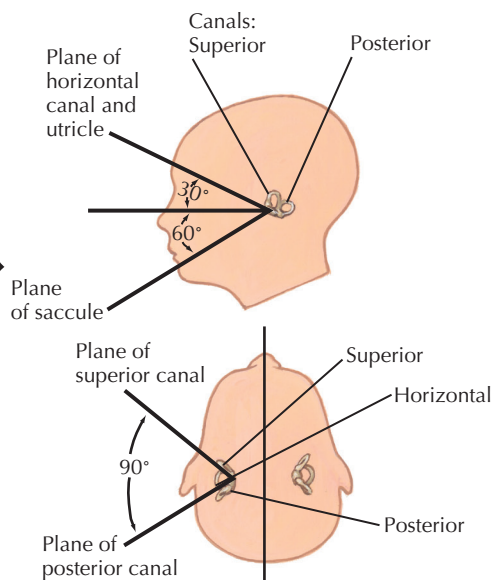
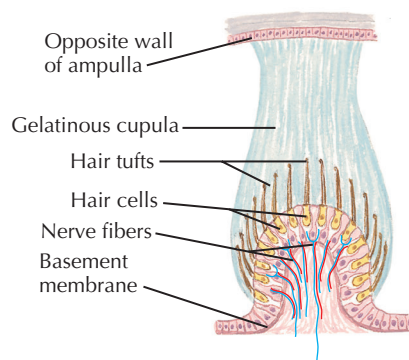
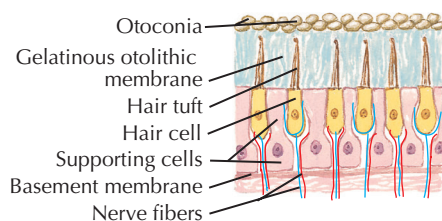
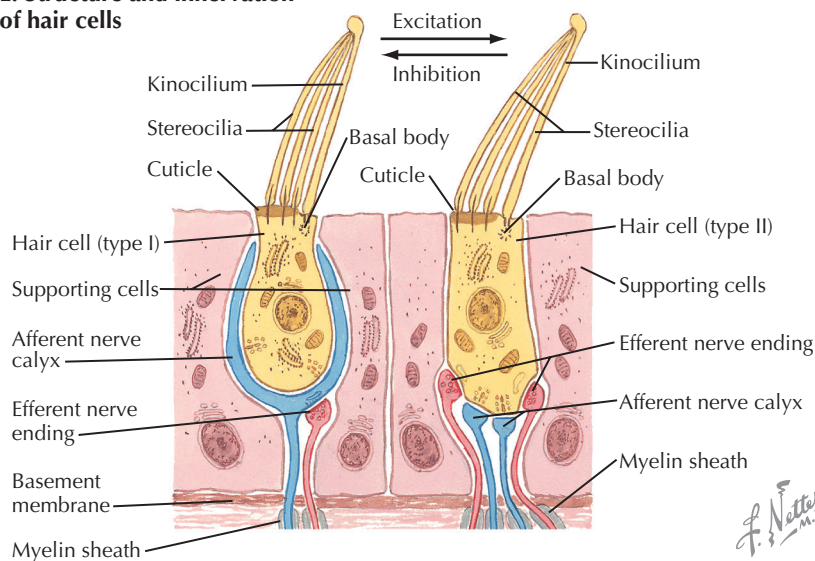
or other sounds). When the nerve is actually destroyed, the tinnitus stops and hearing loss ensues. Auditory nerve damage has symptoms that are present on the ipsilateral side with respect to the damage. In the brain stem, the acoustic striae project axons to a host of nuclei in bilateral fashion, including the superior olivary nuclei, the nuclei of the trapezoid body, the nuclei of the lateral lemnisci, and the inferior colliculi. The inferior colliculi, a mandatory synaptic processing site for central auditory processing, receive information from both ears. These projections proceed to the medial geniculate nucleus and then via the auditory radiations to the auditory cortex (transverse gyrus of Heschl). Damage in the interior of the brain stem or, more likely, in the temporal lobe, generally caused by a vascular infarct, tumor or abscess, or trauma, may result in diminished hearing and auditory neglect from contralateral stimuli but not unilateral deafness.



#### 14.19 CENTRIFUGAL (EFFERENT) AUDITORY PATHWAYS

Descending pathways travel from the auditory cortex, the medial geniculate body of the thalamus, the inferior colliculus, and accessory auditory nuclei of the brain stem to terminate in caudal structures in the pathway, such as the cochlear nuclei and the superior olivary nucleus. These centrifugal connections permit descending control of incoming auditory infor-

mation. The olivocochlear bundle, from the superior olivary nuclei, projects back to the hair cells in the organ of Corti and modulates the transduction process between the hair cells and the primary afferent axons. The motor nuclei of V and VII send LMN axonal projections to the tensor tympani and stapedius muscles, respectively, for reflex dampening of the ossicles in the presence of sustained loud noise.

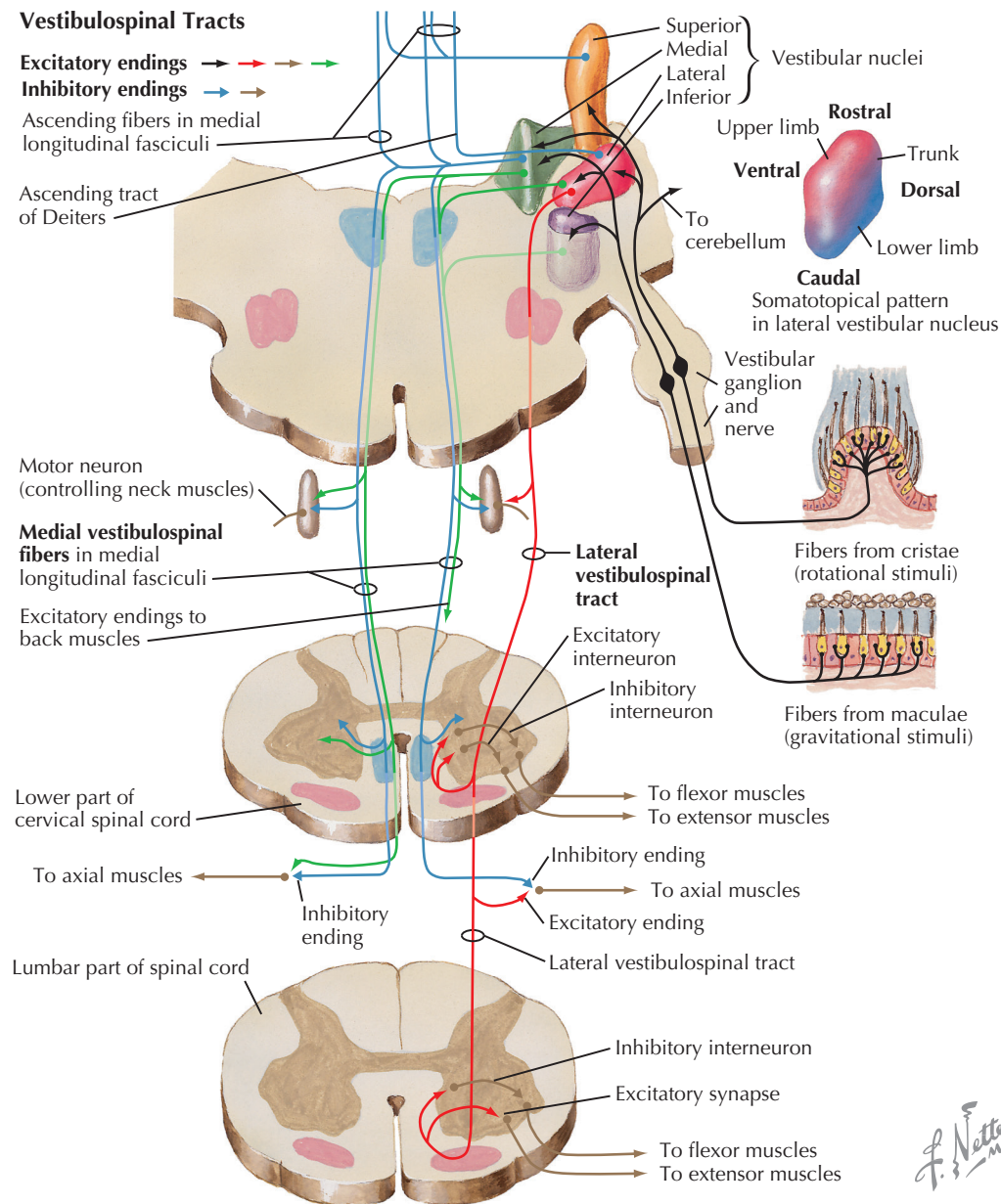
**A. Membranous labyrinth****B. Position within base of skull****C. Section of crista****D. Section of macula****E. Structure and innervation of hair cells****VESTIBULAR SYSTEM****14.20 VESTIBULAR RECEPTORS**

The vestibular receptors include hair cells in the maculae of the utricle (linear acceleration or gravity) and saccule (low frequency vibration) and in the cristae ampullaris of the orthogonally oriented semicircular canals (angular acceleration or movement of the head). Hair tufts from the cristae ampullaris and the maculae are embedded in a gelatinous substance, which is moved when gravity (utricle) exerts force

on the calcium carbonate crystals (otoliths) resting on top of the hairs or when fluid movement occurs in a semicircular canal (head movement). Bending of the kinocilium in the hair tufts depolarizes the hair cell, causing the release of neurotransmitters that stimulate action potentials in primary sensory axons of the vestibular (Scarpa's) ganglion. Additional efferent projections from the CNS modulate this transduction process, similar to centrifugal regulation of auditory transduction.

*F. Netter M.D.*



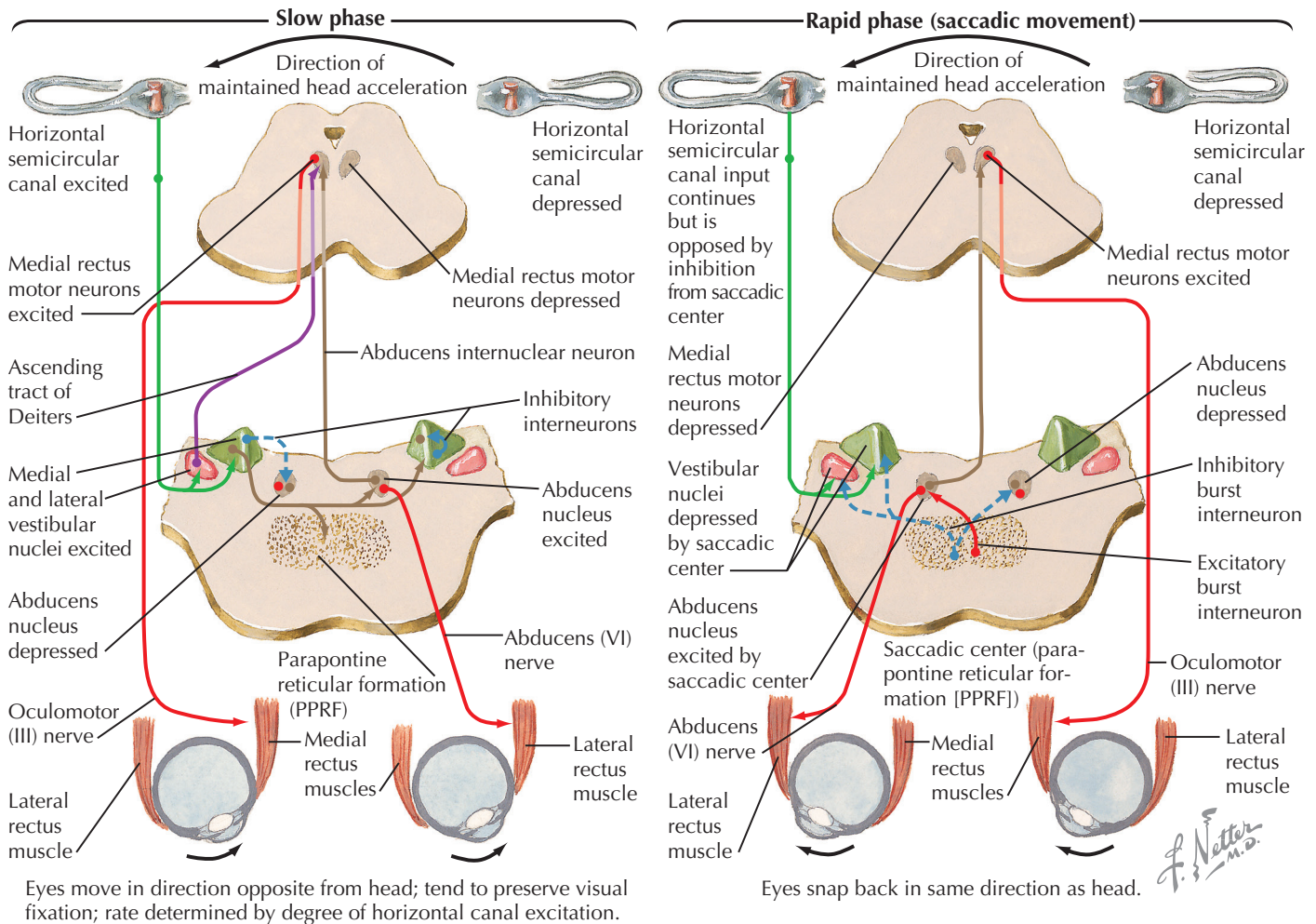


### 14.21 VESTIBULAR PATHWAYS

Primary afferent vestibular axons from the vestibular ganglion terminate in the four vestibular nuclei (superior, inferior, medial, and lateral) and directly in the cerebellum (deep nuclei and cortex). Descending axons are sent via the medial vestibulospinal tract (from the medial nucleus) to spinal cord LMNs that regulate head and neck movements. Descending axons are sent via the lateral vestibulospinal tract (from the lateral nucleus) to all levels of spinal cord LMNs to activate extensor movements. Multiple vestibular nuclei project to the cerebellum to modulate and coordinate muscle activity for basic tone and posture and to extraocular LMNs via the medial longitudinal fasciculus to coordinate eye movements with head and neck movements. Some ascending axons from the vestibular nuclei may reach the thalamus (near the VPM and posterior nuclei), with thalamic projections to the lateral postcentral gyrus (area 2, motion perception and spatial orientation) and to the insular cortex and temporoparietal cortex.

#### CLINICAL POINT

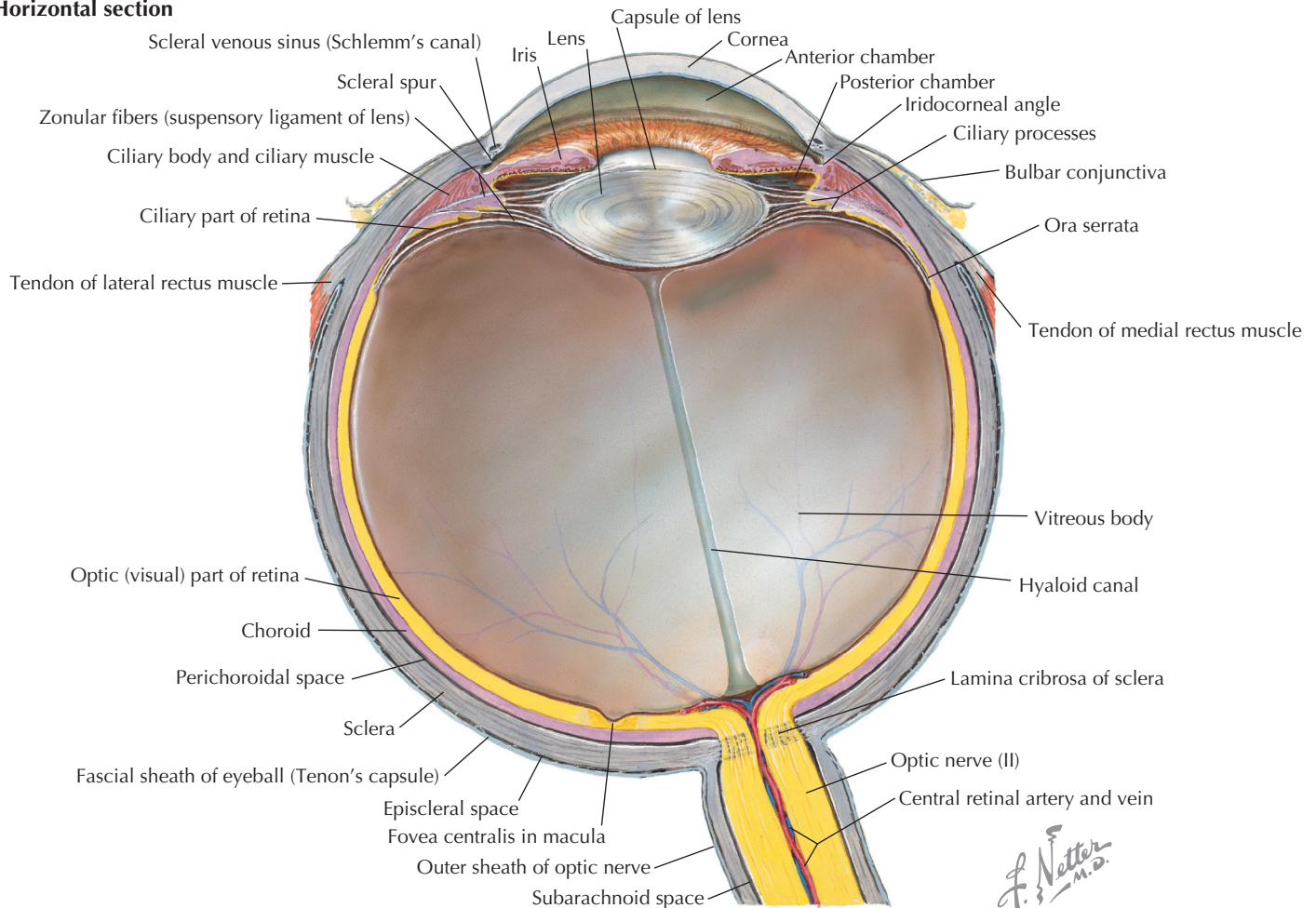
The vestibular nerve consists of axons that supply the hair cells of the cristae in the ampullae of the semicircular canals, as well as the maculae of the utricle and saccule. These primary vestibular axons terminate in the four vestibular nuclei and directly in the vestibular-cerebellum (part of the vermis and flocculonodular lobe). The vestibular nuclei send axonal projections to the LMNs of the spinal cord (via vestibulospinal tracts), the cerebellum, the extraocular nuclei (via the medial longitudinal fasciculus), and the RF. The peripheral vestibular and auditory apparatus can be damaged by increased endolymphatic pressure that gradually destroys hair cells in both the vestibular and auditory peripheral systems. This condition, called Meniere's disease, is characterized by abrupt attacks of severe vertigo that can last for as long as several hours. The attacks are incapacitating and immobilizing and produce nausea and vomiting. The vestibular symptoms are accompanied by auditory symptoms, including tinnitus and progressive sensorineural deafness. Most cases are unilateral, but bilateral disease does occur. After many episodes, some remission is occasionally seen, but the disease can progress to the point where the hearing loss and vestibular damage are almost total.



## 14.22 NYSTAGMUS

Nystagmus is repetitive, alternating back-and-forth movements of the eye, requiring central coordination of extraocular LMNs and eye movements. Optokinetic nystagmus is a normal process of visually activated movement of the eyes via tracking mechanisms, with the eyes returning to a forward position by means of visual association cortex projections through the superior colliculus to extraocular LMNs. Vestibular nystagmus results from asymmetrical input from receptors

in the semicircular canals or from damage to vestibular nuclei or the vestibular cerebellum and is mediated by vestibular projections via the medial longitudinal fasciculus to extraocular nuclei (LMNs); the asymmetrical input provokes the slow phase (or drift) of vestibular nystagmus, eliciting eye movements as if the head were turning. The fast phase (saccadic movement) is the return of the eyes to a forward position, which is provoked when the slow phase moves the eyes to a maximal position.

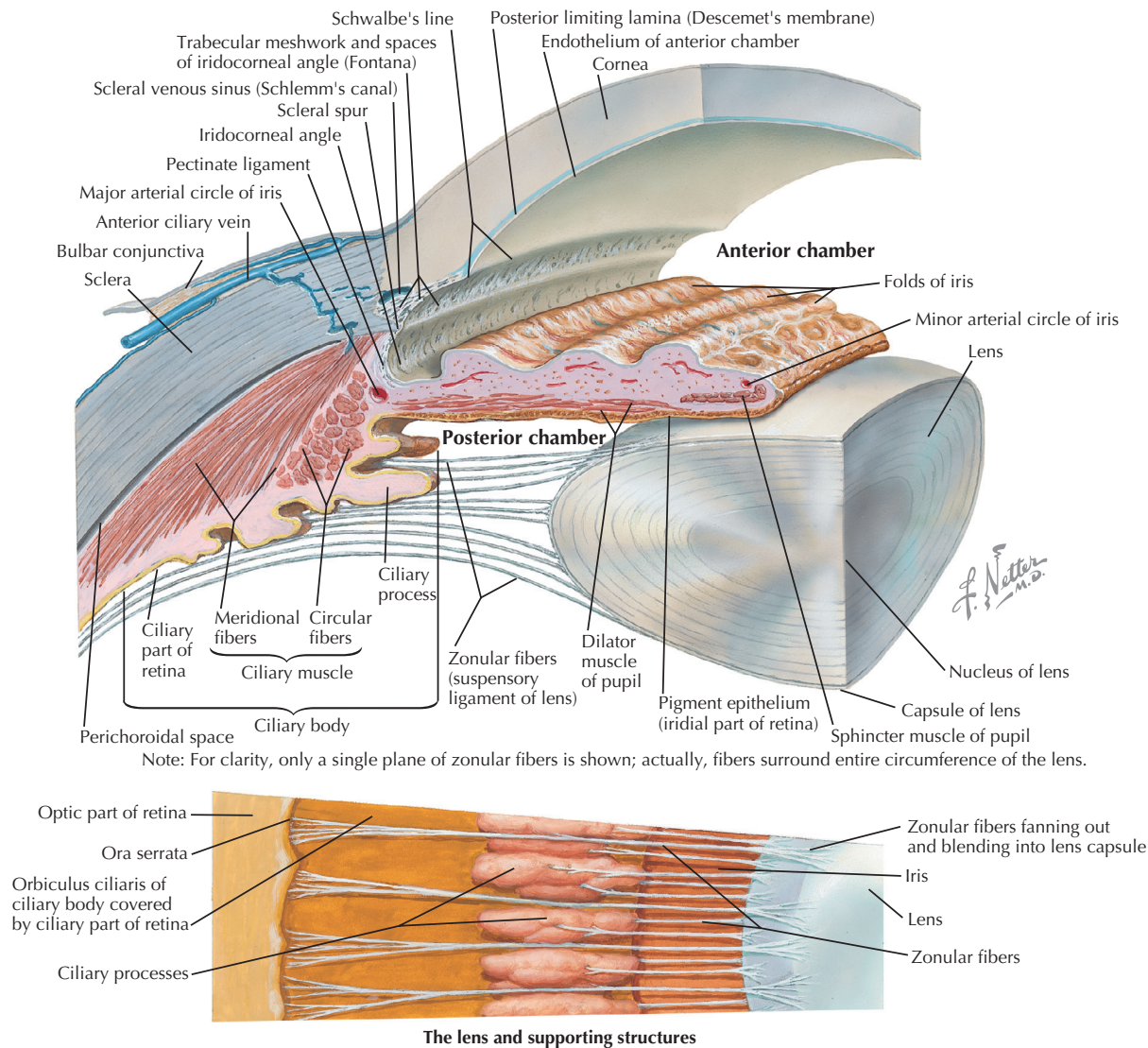
**Horizontal section****VISUAL SYSTEM****14.23 ANATOMY OF THE EYE**

The eye consists of three major layers, or tunics. The outer fibrous layer, the fibrous tunic, consists of the protective cornea (transparent) and the sclera (opaque). The middle layer, the vascular tunic (uvea), consists of the choroid, the ciliary body, and the iris. The transparent biconvex lens, with its surrounding capsule of zonular fibers, is suspended from the ciliary process of the ciliary body. The inner layer, or tunic, consists of the neuroretina, the non-pigment epithelium of the ciliary body, and the pigment epithelium of the posterior iris. The retina contains the photoreceptors for transduction of photon energy from light into neuronal activity. Aqueous humor is secreted from blood vessels of the iris into the posterior chamber and flows through the aperture of the pupil into the anterior chamber, where it is absorbed into the trabecular meshwork into Schlemm's canal at the iridocorneal angle. Blockage of this absorption of aqueous humor results in glaucoma. The vitreous humor fills the interior of the eyeball.

**CLINICAL POINT**

When light impinges on the eye, it is refracted to focus on the photoreceptors of the retina to permit interpretation of the outside visual world. A vast proportion (close to 90%) of the refraction of light is accomplished by the cornea. A smaller percentage (approximately 10%) of the refraction is accomplished by the lens; however, this smaller percentage can be regulated neurologically, via CN III and its influence on accommodation to near vision. If the cornea is opacified (e.g., following abrasion that results in vascularization) it may impede the light pathway and cause a distortion of vision. Accommodation to near vision occurs when one tries to look at an object that is close rather than distant and usually involves simultaneous convergence, constriction (pupil), and accommodation. Accommodation involves a portion of the nucleus of Edinger-Westphal, which acts through CN III axonal projections to the ciliary ganglion. This portion provides postganglionic parasympathetic cholinergic innervation to the ciliary muscle. When this parasympathetic system is activated, the ciliary muscle lifts up and in, releasing tension on the zonular fibers that suspend the lens, permitting the lens to bunch up (fatten) and refract light. Accommodation commonly diminishes with age (presbyopia). A CN III palsy damages both pupillary constriction (resulting in a fixed, dilated pupil) and accommodation to near vision. Accommodation also can be damaged by trauma, diabetes, viral infections, and other pathology. If accommodation is impaired, corrective lenses are needed to allow proper focusing of light on the retina.





The lens and supporting structures

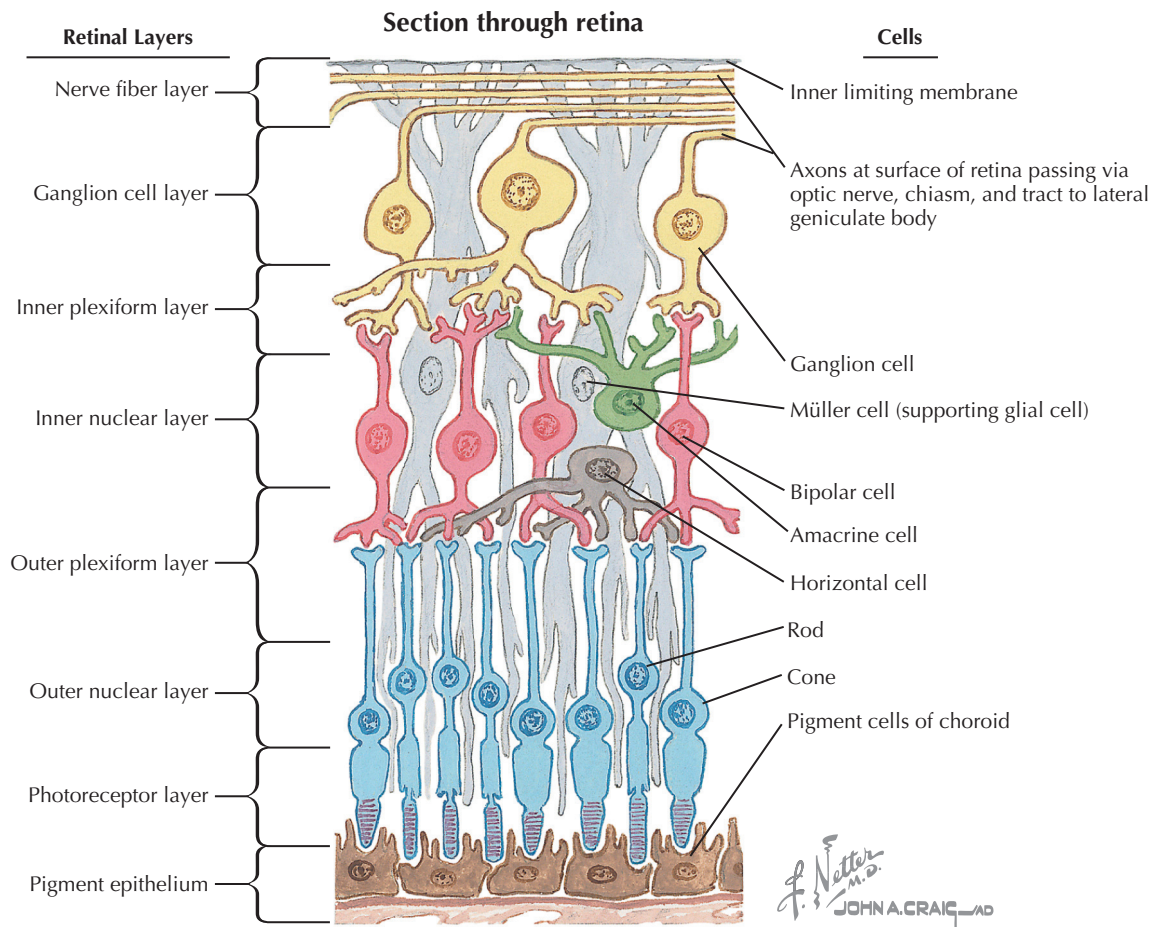
#### 14.24 ANTERIOR AND POSTERIOR CHAMBERS OF THE EYE

The ciliary muscle and the pupillary constrictor muscle are supplied by parasympathetic postganglionic myelinated nerve fibers from the ciliary ganglion (innervated by preganglionics in the nucleus of Edinger-Westphal in CN III). Contraction of the ciliary muscle reduces the tension on zonular fibers and causes the lens to curve or bunch, which induces accommodation for near vision. The pupillary constrictor muscle also is supplied by parasympathetic postganglionic fibers from the ciliary ganglion. In the pupillary light reflex, light shone into one eye stimulates photoreceptors and related neurons in the retina; retinal ganglion cells send neural projections via the optic (II) nerve (afferent limb), which terminate in the pretectum. Neurons of the pretectum project bilaterally (crossed axons through the posterior commissure) to the Edinger-Westphal nucleus. This nucleus projects to the ciliary ganglion via CN III (efferent limb), which causes both direct (ipsilateral) and consensual (contralateral) pupillary constriction. The pupillary dilator muscle is supplied by sympathetic postganglionic unmyelinated nerve fibers from the superior cervical ganglion (innervated by preganglionics in T1 and T2). Schlemm's canals are conspicuous at the iridocorneal angle.

The lens is surrounded by a capsule anchored and suspended by an array of zonular fibers fanning out in circular fashion to attach to the ciliary processes of the ciliary body. Some interior zonular fibers extend along the ciliary body to the junction at the ora serrata.

#### CLINICAL POINT

Aqueous humor is secreted from the vasculature of the ciliary apparatus into the posterior chamber. It circulates through the pupillary aperture into the anterior chamber. From the anterior chamber, the aqueous humor is resorbed into the scleral venous sinuses, called the canals of Schlemm. If the canals of Schlemm are blocked, preventing absorption of aqueous humor, increased ocular pressure occurs; this results in pressure on the optic nerve head, cupped discs, atrophy, and defective vision of increasing severity, including total blindness. Glaucoma, the most common cause of optic nerve damage, occurs in more than 1% of the population over 40 years of age. This condition can be detected through ophthalmoscopy and tonometry. The principal type of glaucoma is called wide-angle glaucoma, which involves gradual sclerosis of the canals of Schlemm. A far less common type of glaucoma is narrow-angle (acute or closed-angle) glaucoma, a medical emergency in which bunching of the dilator muscle or narrowing of the iridocorneal angle blocks resorption of aqueous humor. The eye is red, swollen, and painful, sometimes causing a headache. It can be precipitated by pupillary dilation during an ophthalmological examination and must be reversed by means of pharmacological pupillary constriction.



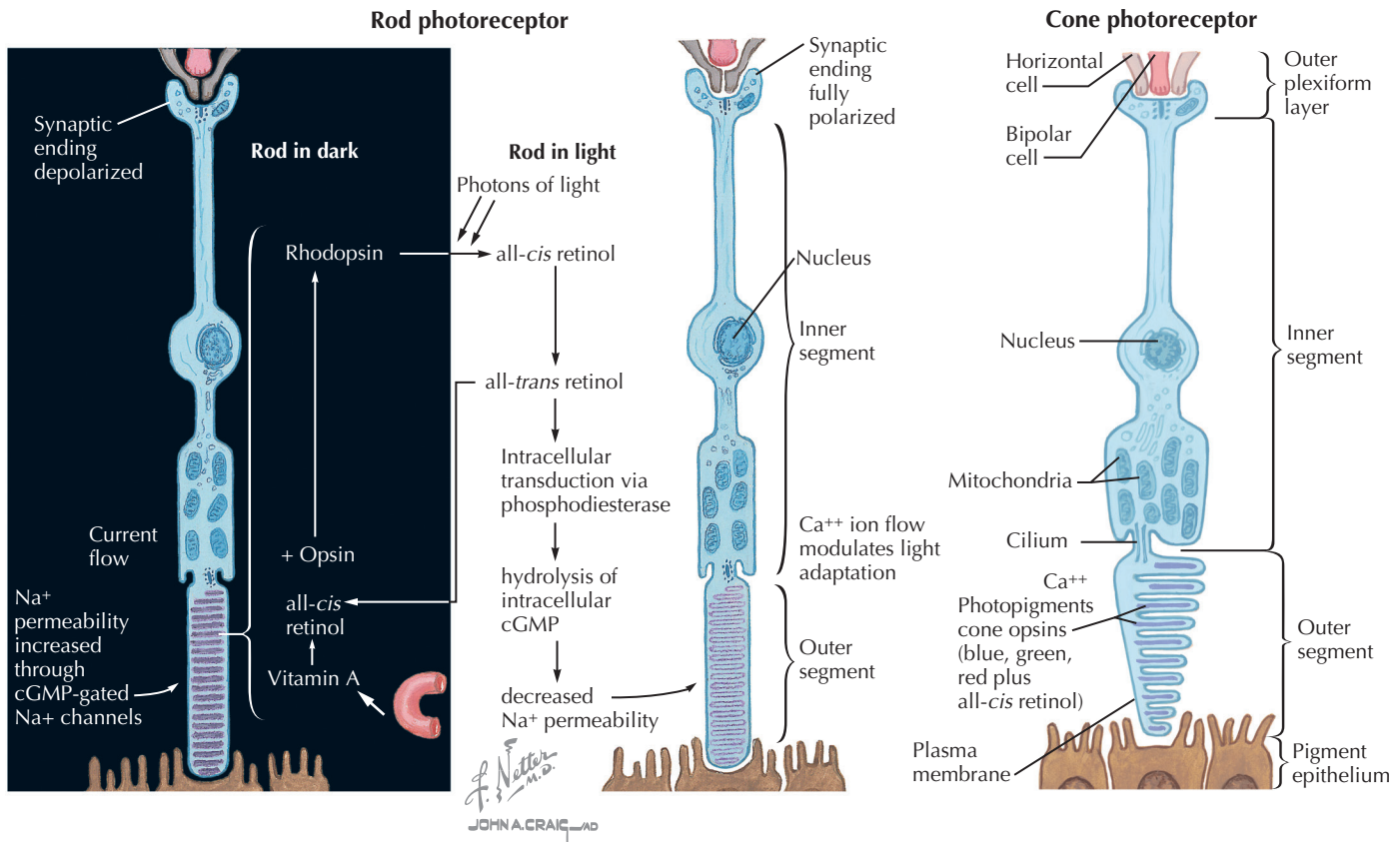
### 14.25 THE RETINA: RETINAL LAYERS

The retina is a tissue-paper-thin piece of CNS tissue that contains the photoreceptors; it is attached to the vascular tunic at the ora serrata. The layers of the retina in the interior of the eyeball are oriented from outer to inner. The pigment epithelium is at the outer margin, followed by the outer nuclear layer (photoreceptors), the inner nuclear layer (bipolar neurons, amacrine and horizontal cells), and the ganglion cell layer. The outer and inner plexiform layers are the zones of synaptic connectivity. The ganglion cell axons form an inner nerve fiber layer projecting centrally toward the optic nerve head, into which they collect as the optic nerve, CN II. The outer segments of the photoreceptors, the rods and cones, are embedded in a pigment epithelium in the outer part of the interior eyeball to prevent backscatter of light. The rods and cones connect synaptically with bipolar cells in the outer plexiform layer; these bipolar neurons connect with the ganglion cells of the retina in the inner plexiform layer. The retinal ganglion cells are the equivalent of secondary sensory nuclei for other sensory modalities. Horizontal and amacrine cells provide horizontal interconnections in the retina, mainly at the outer plexiform layer and the inner plexiform layer, respectively. These cells modulate the central flow of information from the photoreceptors to the bipolar neurons to the retinal ganglion cells. The central point for visual focusing is the fovea centralis (0.4 mm in diameter) in the macula (3 mm in diameter), which is found temporally and slightly below the geo-

metric midpoint. The fovea consists purely of cones for color vision (photopic); these cone projections to ganglion cells involve very little convergence. In the fovea, there is close to a one-to-one-to-one relationship among the cones, bipolar neurons, and ganglion cells. The peripheral retinal photoreceptors are mainly rods, for night vision (scotopic); there is huge convergence of rods onto bipolar neurons, which in turn converge onto single ganglion cells. Thus, acuity is best achieved in the fovea, the region for color vision.

#### CLINICAL POINT

Cones permit color vision and are concentrated in the macula of the retina, the point of focus for high-acuity vision. The center of the macula, the fovea centralis, consists entirely of cones. These cones are connected with bipolar retinal cells, which in turn contact retinal ganglion cells, resulting in conveyance of visual information via the optic nerve into other CNS structures (superior colliculus, pretectum, hypothalamus, lateral geniculate nucleus). The macular pathway is essential for photopic (color, high-acuity) vision. The peripheral retina contains rods as the main photoreceptors; rods massively converge onto bipolar neurons. This peripheral retinal pathway is active in scotopic (night) vision. The macula can undergo a gradual process of depigmentation and degeneration in elderly individuals, leading to the loss of central vision and reading capability. Although there is no immediate cure for macular degeneration, carotenoid supplements of lutein and zeaxanthin appear to replenish the macula with these important depleted carotenoids, slowing the degenerative process. Although macular degeneration is mainly a disease of the elderly, some young individuals with inherited storage diseases (Tay-Sachs) or infectious processes may experience macular degeneration.



## 14.26 THE RETINA: PHOTORECEPTORS

Rods use the photopigment rhodopsin to achieve transduction of photons of energy from light into neurotransmitter release that can activate electrical activity in bipolar neurons. Rod light transduction involves conversion of all-*cis*-retinal (from rhodopsin) to an all-*trans* form, provoking calcium influx and a decrease in sodium conductance with hyperpo-

larization. This process is outlined in detail in the first two parts of the figure, a rod in the dark and a rod in light. When a rod is activated by light, it hyperpolarizes rather than depolarizes. A cone uses opsin photopigments for blue, green, and red, as well as all-*cis* retinal; these cone pigments permit color vision.

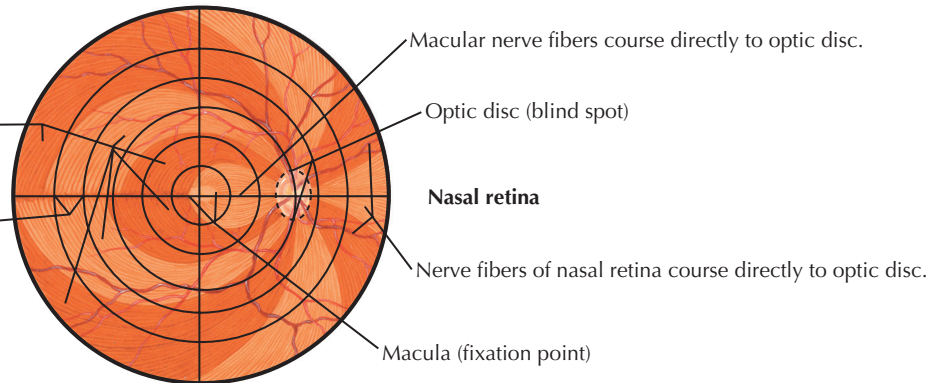


### A. Topography of retinal nerve fibers

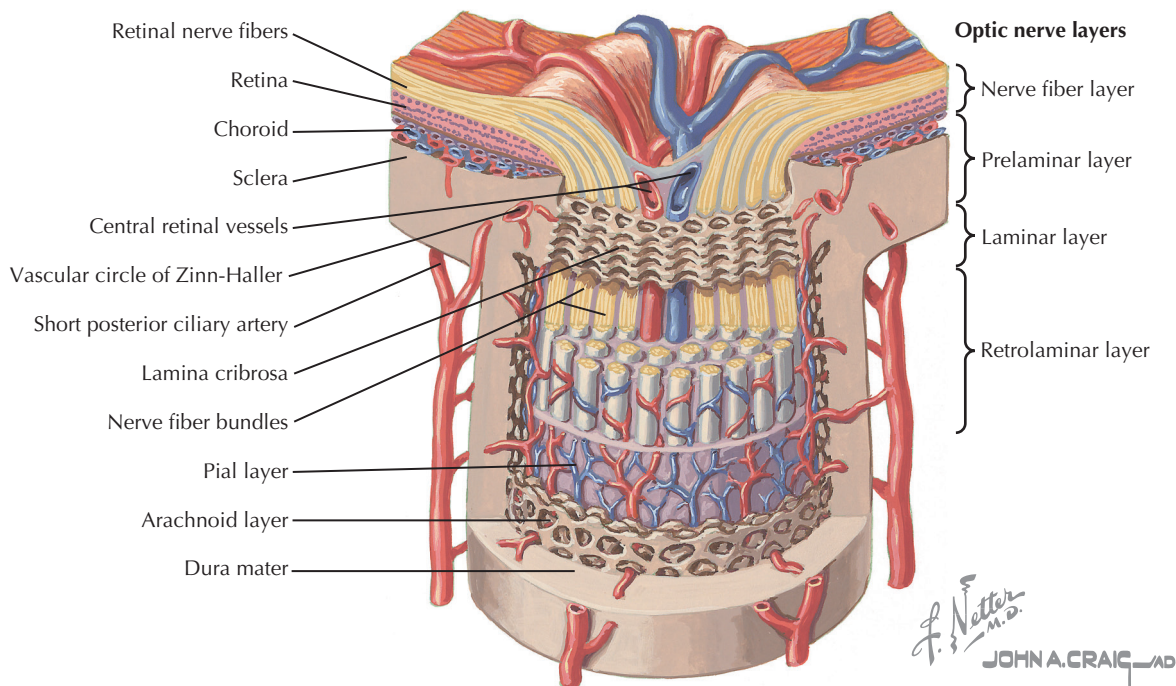
Arcuate nerve fibers from temporal periphery of retina must arc around macular bundle.

#### Temporal retina

Median horizontal raphe. Inferior and superior arcuate fibers meet but do not cross.



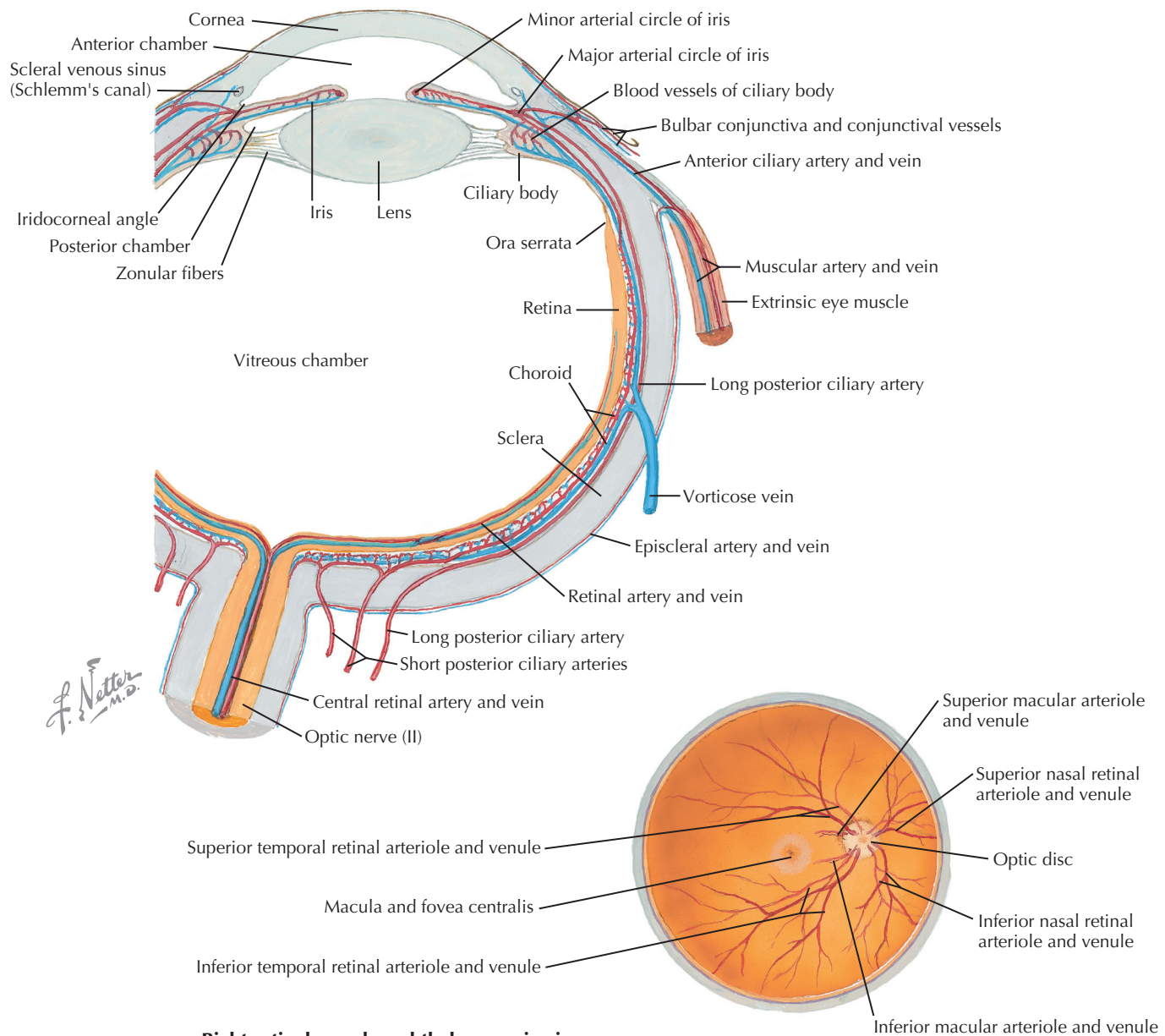
### B. Anatomy of optic nerve



## 14.27 THE RETINA: OPTIC NERVE

**A,** The retina is topographically organized; a representation of the visual world (referred to as a visual field) is mapped onto the retina of each eye. Because the eye acts like a camera, the visual world is inverted as it projects onto the retina. The temporal (lateral) visual field falls on the nasal hemiretina, and the nasal (medial) visual field falls on the temporal hemiretina. The upper visual field falls on the lower hemiretina, and the lower visual field falls on the upper hemiretina. When viewing the retina directly using ophthalmoscopy, the macula is located temporally and slightly inferior to the geometric midpoint of the retina. The optic disc (zone of optic nerve fibers, sometimes called the blind spot) is located nasally and slightly above (superior to) the geometric midpoint. The precise retinotopic organization is maintained throughout the projections of the main visual pathway (the retino-geniculo-

calcarine pathway). **B,** The optic nerve (CN II) is a CNS tract that consists of myelinated axons of the ganglion cells of the retina. These axons collect across the innermost layer of the neuroretina and form the optic nerve, which exits from the eyeball nasally, slightly above the horizontal midline. These optic nerve fibers are myelinated by oligodendroglia. The optic nerve is surrounded by meninges, as part of the CNS. A subarachnoid space containing cerebrospinal fluid is present between the arachnoid and pial layers of the meninges. Elevated intracranial pressure can exert pressure on the optic nerve head (where the ganglion cell axons first form the optic nerve), forcing it inward; this phenomenon is called papilledema and is evidence of increased intracranial pressure; approximately 24 hours are required for increased intracranial pressure to cause papilledema. Major retinal vessels from the central retinal artery and vein travel in the optic nerve.



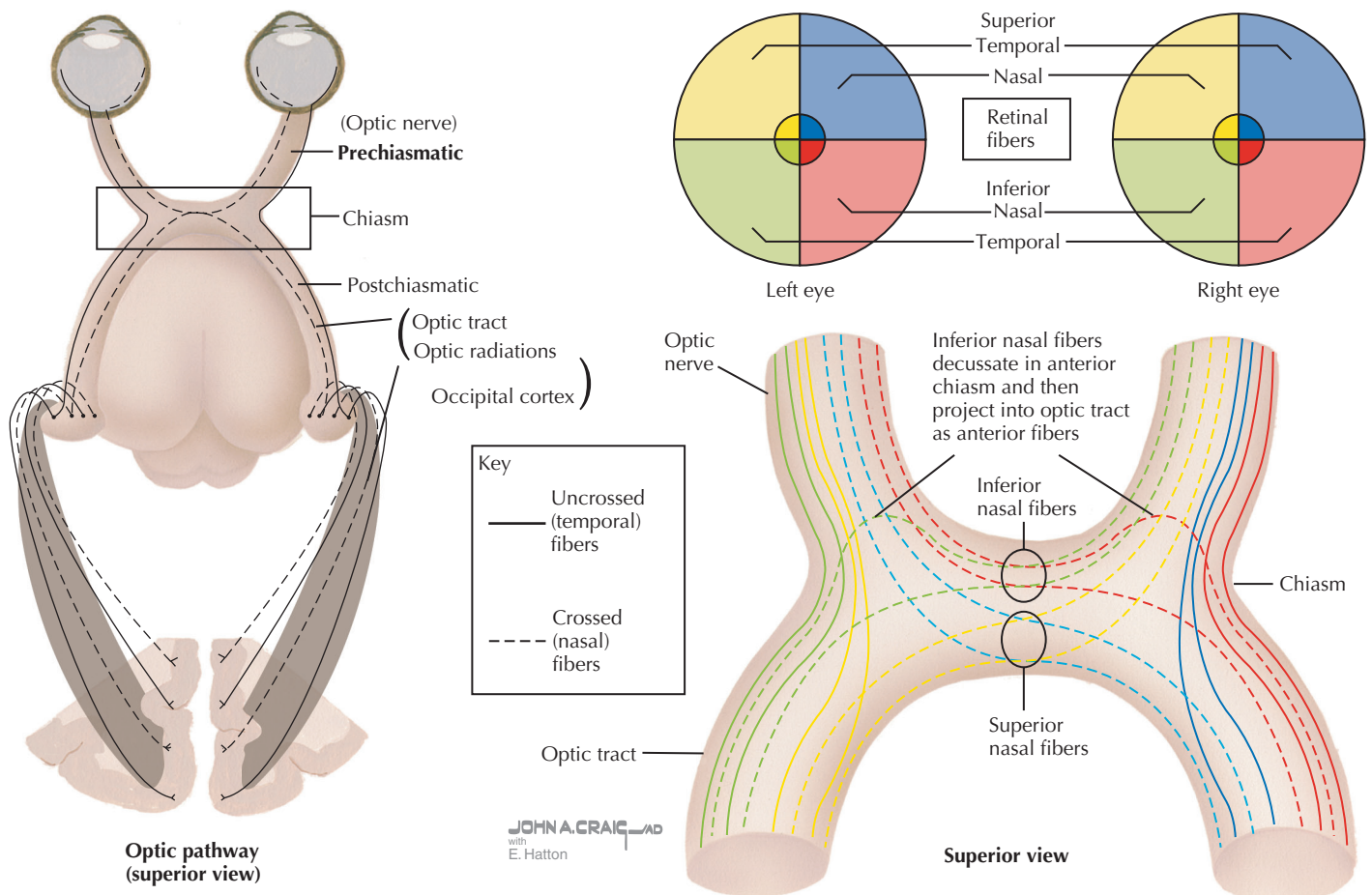
**Right retinal vessels: ophthalmoscopic view**

### 14.28 ARTERIES AND VEINS OF THE EYE

The central retinal artery and its branches supply blood to the retina. This arterial system, derived from the ophthalmic artery (the first branch off the internal carotid artery), is commonly the first site where ischemic or embolic events (transient ischemic attacks) herald the presence of serious vascular disease and high risk for a future stroke. Ciliary arteries supply the middle vascular tunic, which also contributes partial blood supply to the retina; this component of blood supply can be disrupted by a detached retina. Blood vessels enter and exit the retina at the optic disc (nerve head), located nasally and slightly superiorly from the geometric midpoint of the eyeball. The macula is located temporally and slightly inferiorly from this midpoint.

#### CLINICAL POINT

The central retinal artery is a common site of emboli in impending cerebrovascular disease; such emboli are forerunners of stroke and indications of carotid atherosclerosis or occlusion. An embolus in the central retinal artery may produce temporary (fleeting) blindness in the affected eye, called amaurosis fugax, which lasts for several minutes but less than an hour; such an episode is called a transient ischemic attack. An infarct in the central retinal artery produces characteristic ophthalmologic findings, such as loss of opalescence in the fovea (a so-called cherry-red spot). If the central retinal vein is occluded, a hemorrhage is seen, and the resultant visual loss may be significant. In addition to hemorrhages, edema and exudates may be present, indicative of hypertension or diabetic problems. If the retina becomes detached, it may be separated from part of its blood supply from the ciliary arteries in the middle vascular tunic, which also results in loss of vision.

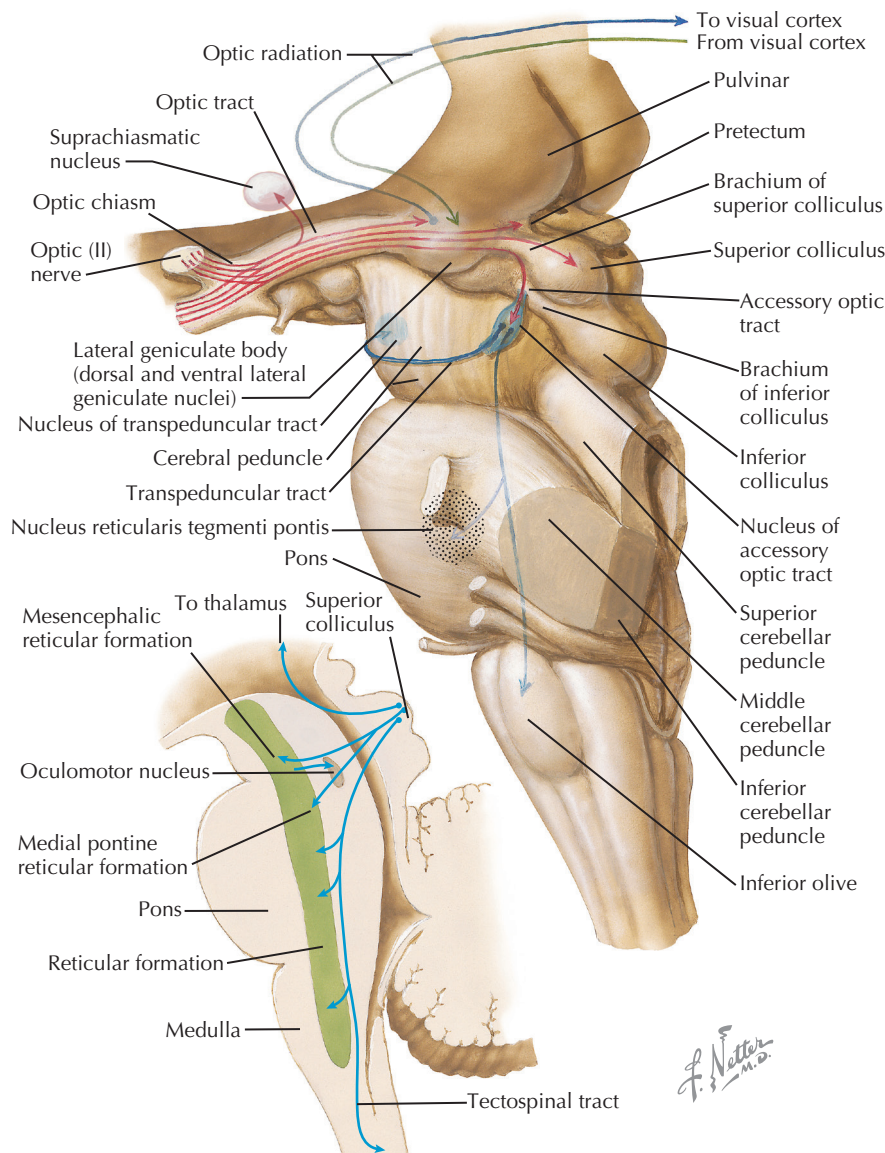


#### 14.29 ANATOMY AND RELATIONSHIPS OF THE OPTIC CHIASM

Axons from ganglion cells in the temporal hemiretinas (carrying information from the nasal visual fields) travel into the optic nerve and remain ipsilateral in the optic chiasm; they synapse in the ipsilateral lateral geniculate body or nucleus. Axons from ganglion cells in the nasal hemiretinas (carrying information from the temporal visual fields) travel into the optic nerve and cross the midline in the optic chiasm; they synapse in the contralateral lateral geniculate body. Therefore,

crossing axons in the optic chiasm carry information from the temporal visual fields, which are derived from retinal ganglion cells in the nasal hemiretinas. These crossing axons are susceptible to disruption by a pituitary adenoma; such a lesion can produce a bitemporal hemianopia, starting first as an upper visual quadrant defect and progressing to full hemianopia. The optic tract contains axons from the ipsilateral temporal hemiretina and the contralateral nasal hemiretina, representing the contralateral visual field; disruption of the optic tract results in contralateral hemianopia.





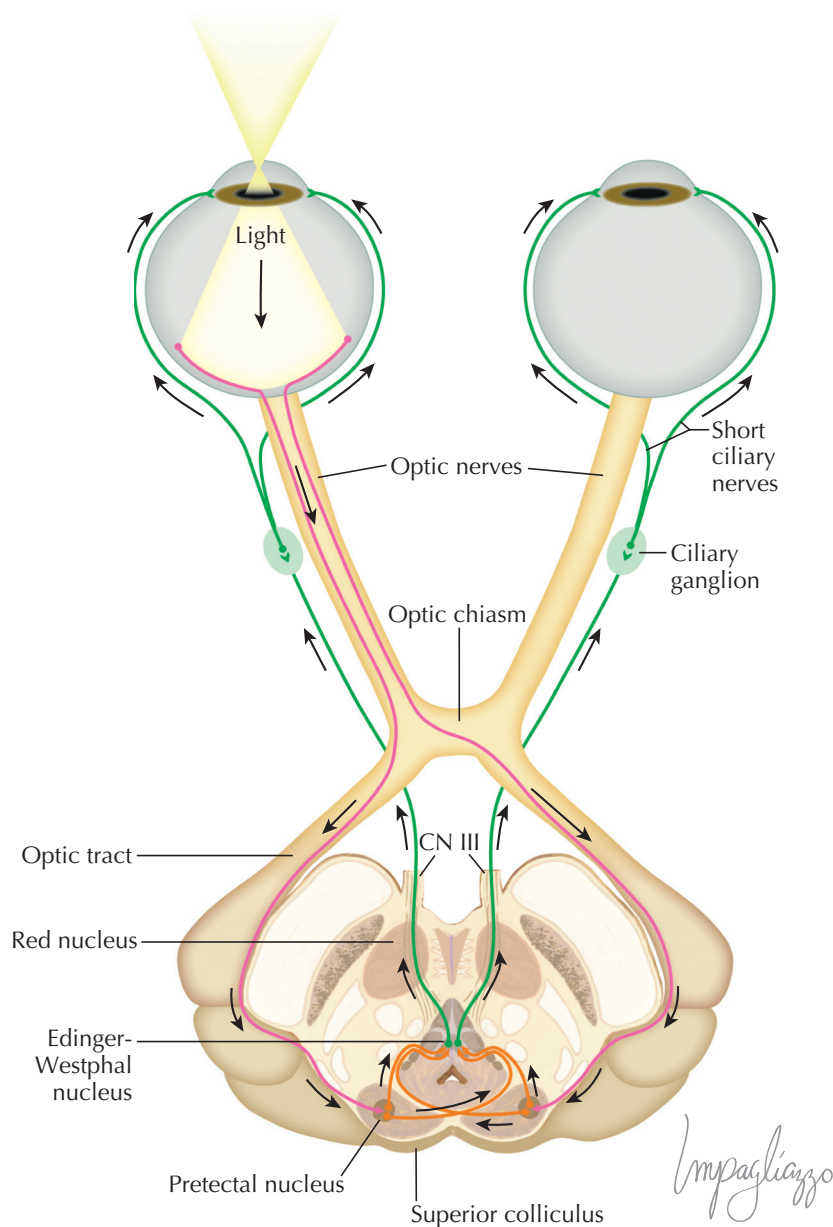
### 14.30 VISUAL PATHWAYS: RETINAL PROJECTIONS TO THE THALAMUS, HYPOTHALAMUS, AND BRAIN STEM

Retinal projections travel through the optic nerve, chiasm, and tract and terminate in several regions, including the lateral geniculate body or nucleus, the upper layers of the superior colliculus, the pretectum, the hypothalamus (suprachiasmatic nucleus), and the nucleus of the accessory optic tract. The lateral geniculate body mediates conscious visual interpretation of visual input via the retino-geniculo-calcarine (area 17) pathway. The superior colliculus provides a second visual pathway through projections to the pulvinar, which in turn projects to the associative visual cortex (areas 18 and 19), providing localizing information for coordinating movement of the eyes to novel or moving visual stimuli. Neurons in deeper layers of the superior colliculus also provide descending contralateral connections (tectospinal tract) to cervical LMNs to mediate reflex visual effects on head and neck movements; collaterals of this descending system terminate in the brain stem reticular formation. The superior colliculus receives input from the visual cortex. The pretectum mediates the pupillary light reflex. The suprachiasmatic nucleus of the hypothalamus

integrates light flux and regulates circadian rhythms and diurnal cycles. The nucleus of the inferior accessory optic tract may help to mediate brain stem responses for visual tracking and may interconnect with sympathetic preganglionic neurons in T1 and T2 (regulating the superior cervical ganglion).

#### CLINICAL POINT

Ganglion cells of the retina (the neural equivalents of the secondary sensory nuclei in other sensory systems, such as the nuclei gracilis and cuneatus) send projections through the optic nerve, chiasm, and tract to terminate in the superior colliculus, the lateral geniculate nucleus of the thalamus, the pretectum, the suprachiasmatic nucleus of the hypothalamus, and some brain stem sites. However, they all require the projection of axons through the optic nerve, chiasm, and tract. If the optic nerve is damaged (by multiple sclerosis, glaucoma, inflammatory disorder, trauma, vascular pathology), there is visual loss in a selected area (scotoma) or in the entire ipsilateral eye (monocular blindness). If the optic chiasm is damaged, usually by a pituitary tumor, the growth of the tumor impinges on the crossing fibers in a manner that disrupts the outer visual fields (bitemporal hemianopia), usually from the upper to the lower fields (much like pulling down the shades). If the optic tract is damaged, axons from the ipsilateral temporal hemiretina and the contralateral nasal hemiretina are disrupted, producing a contralateral visual field deficit (homonymous contralateral hemianopia).



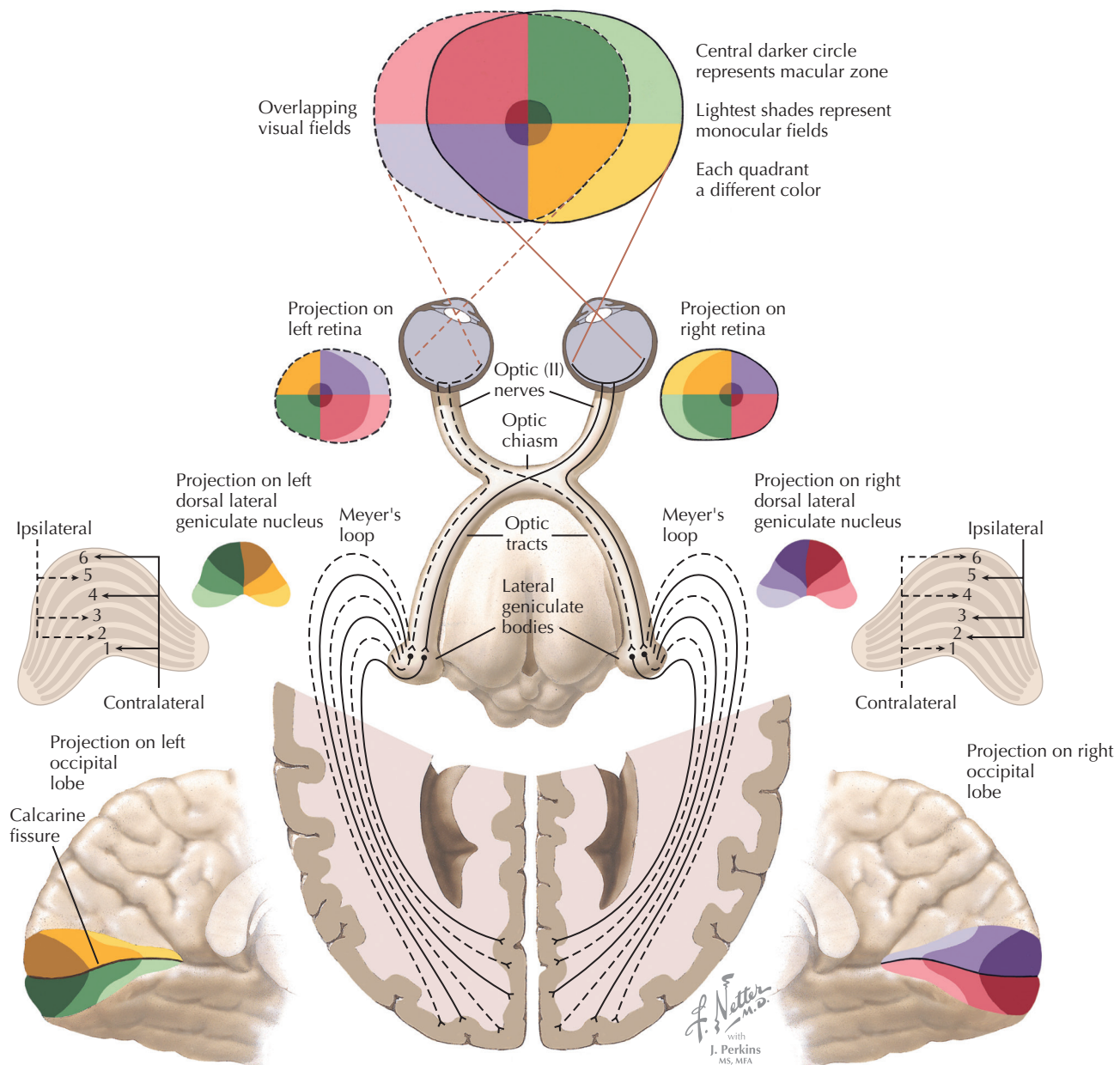
### 14.31 PUPILLARY LIGHT REFLEX

The pupillary light reflex requires CN II, CN III, and central brain stem connections. Light shined in one eye stimulates retinal photoreceptors, and subsequently retinal ganglion cells, whose axons travel through the optic nerve, chiasm, and tract to terminate in the pretectum (pretectal nucleus). The pretectal neurons project to a portion of the nucleus of Edinger-Westphal on both sides. This preganglionic parasympathetic nucleus projects to ciliary ganglion neurons, which in turn send postganglionic axons to innervate the pupillary constrictor muscle. Thus, light shined in one eye

normally results in the constriction of both pupils (ipsilateral pupillary constriction—direct response; contralateral pupillary constriction—consensual response).

Lesions of CN II produce an unresponsive pupillary light reflex on both sides (afferent pupillary defect) from light shined in the eye on the side of the CN II lesion. With light shined in the unaffected eye, both pupils constrict.

Lesions of CN III result in unresponsive ipsilateral pupillary constriction on the affected side (the pupil is “fixed and dilated”) when light is shined in either eye (efferent pupillary defect).



### 14.32 VISUAL PATHWAY: THE RETINO-GENICULO-CALCARINE PATHWAY

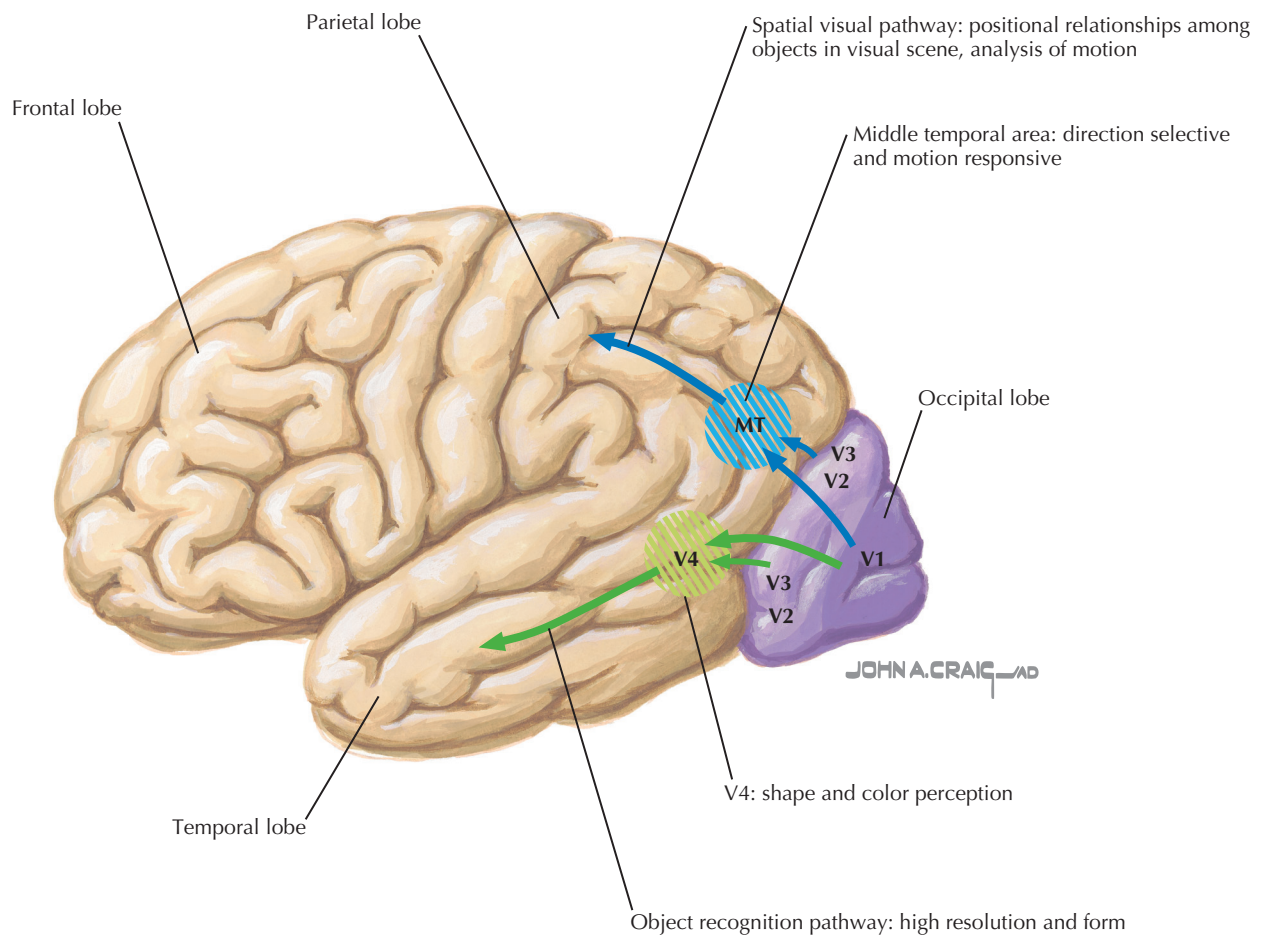
The retino-geniculo-calcarine pathway conveys information about fine-grained conscious visual analysis of the outside world. It is organized topographically (retinotopic) throughout its course to the calcarine (visual) cortex in the occipital lobe. The nasal hemiretinal ganglion cell axons cross the midline in the optic chiasm, whereas the temporal hemiretinal ganglion cell axons remain ipsilateral. Thus, each optic tract conveys information from the contralateral visual world (or visual field); damage to the optic tract produces contralateral hemianopia. The optic tract terminates in the lateral geniculate body or nucleus and is organized in 6 layers, as shown. However, binocular convergence does not take place here; ganglion cell axons from the ipsilateral temporal hemiretina terminate in layers 2, 3, and 5, and ganglion cell axons from the contralateral nasal hemiretina terminate in layers 1, 4, and 6. The optic radiations project to the calcarine (striate) cortex (area 17, the primary visual cortex). A portion of the optic

radiations loops through the temporal lobe (Meyer's loop) and can be damaged by a tumor or mass, resulting in contralateral upper quadrantanopia. Bilateral convergence from right and left retinas first takes place in the primary visual cortex, area 17. The retinotopic organization of this pathway is shown in color in this illustration.

#### CLINICAL POINT

Meyer's loop consists of axons of the lateral geniculate nucleus that loop downward through the temporal lobe before extending posteriorly to synapse on cortical neurons in layer 4 of the lower bank of the ipsilateral calcarine fissure (area 17, primary visual cortex). The temporal lobe is a site at which tumor or abscess formation is far more likely than it is in the parietal or occipital lobes. If such a mass lesion damages fibers of Meyer's loop, the individual loses vision in the upper quadrant of the contralateral visual field (upper contralateral quadrantanopia), reflecting the persistent "retinotopic" organization of the entire retino-geniculo-calcarine pathway that is depicted in this illustration. This visual deficit is sometimes referred to as a "pie in the sky" deficit.



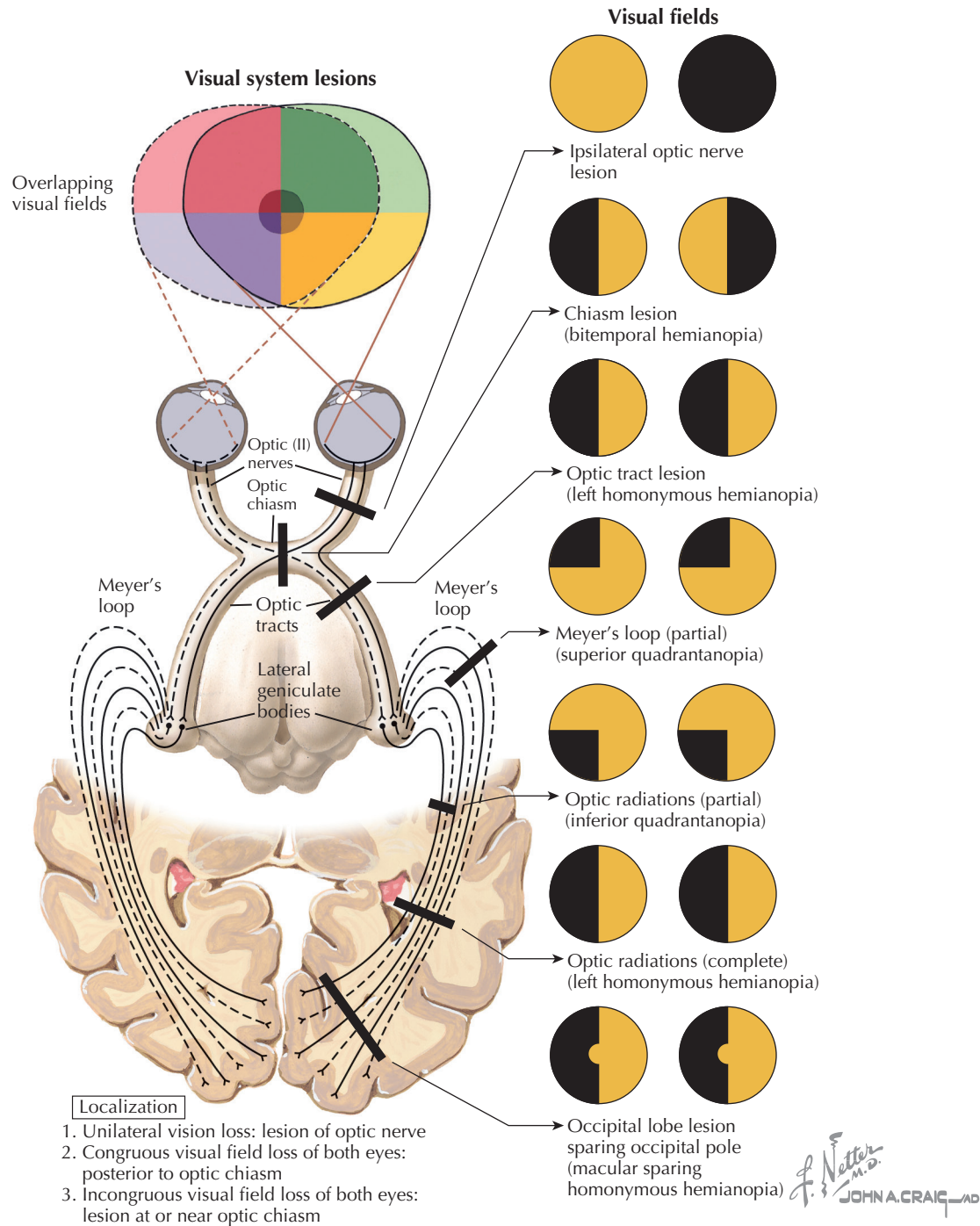


### 14.33 VISUAL PATHWAYS IN THE PARIETAL AND TEMPORAL LOBES

Neurons in the primary visual cortex (V1, area 17) send axons to association visual cortices (V2 and V3, areas 18 and 19). V2 and V3 also receive input from the superior colliculus via the pulvinar. V1, V2, and V3 project to the middle temporal (MT) area and V4. Middle temporal neurons are direction selective and motion responsive, and further project into the parietal lobe for spatial visual processing. The parietal neurons provide analysis of motion and positional relationships among objects in the visual field. V4 neurons are involved in shape and color perception. Neurons in V4 project into the temporal lobe, in which further neuronal processing provides high-resolution object recognition, including faces, animate and inanimate objects, and the classification and orientation of objects. Small infarcts in the temporal lobe may produce specific agnosias, inability to recognize specific types of objects, such as faces or animate objects.

#### CLINICAL POINT

The retino-geniculo-calcarine pathway projects to area 17, the primary visual cortex; subsequent axonal projections are sent to areas 18 and 19. In these visual-association cortices, feature extraction from simple to complex to hypercomplex cells occurs, giving form to new visual information. A parietal cortical pathway further processes information related to the direction and motion of objects—a spatial visual pathway. A temporal cortical pathway conveys further information about the shape, color, and form of objects. Some discrete lesions in these parietal and temporal cortical pathways can produce distinctive visual deficits. Visual agnosias occur when an individual cannot recognize objects that are viewed but has full visual acuity. This can happen with lesions in the occipito-temporal visual pathway. Visual agnosias are particularly common with lesions in the dominant mesial portion of the occipital cortex; they accompany a right homonymous hemianopia. Cortical color agnosias (cortical color blindness) also can occur with lesions in the occipito-temporal visual pathway, through V4. Some specific lesions of the occipito-temporal pathway, especially when bilateral, can result in prosopagnosia, the inability to recognize faces. Some lacunar infarcts in this pathway also may result in the inability to distinguish between animate and inanimate objects. Lesions in the occipito-parietal visual pathway, particularly in the nondominant hemisphere, can cause visual-spatial disorientation, appearing clinically as impaired ability to see.



### 14.34 VISUAL SYSTEM LESIONS

Lesions of the optic nerve, optic chiasm, optic tract, Meyer's loop in the temporal lobe, optic radiations, and visual cortex produce specific visual-field deficits, as shown in this figure.

# 15

## MOTOR SYSTEMS

### Lower Motor Neurons

- 15.1 Alpha and Gamma Lower Motor Neurons
- 15.2 Distribution of Lower Motor Neurons in the Spinal Cord
- 15.3 Distribution of Lower Motor Neurons in the Brain Stem

### Upper Motor Neurons

- 15.4 Cortical Efferent Pathways
- 15.5 Color Imaging of Cortical Efferent Pathways
- 15.6 Corticobulbar Tract
- 15.7 Corticospinal Tract
- 15.8 Corticospinal Tract Terminations in the Spinal Cord
- 15.9 Rubrospinal Tract
- 15.10 Vestibulospinal Tracts
- 15.11 Reticulospinal and Corticoreticular Pathways
- 15.12 Tectospinal Tract and Interstitiospinal Tract
- 15.13 Spinal Cord Terminations of Major Descending Upper Motor Neuron Tracts
- 15.14 Central Control of Eye Movements
- 15.15 Central Control of Respiration

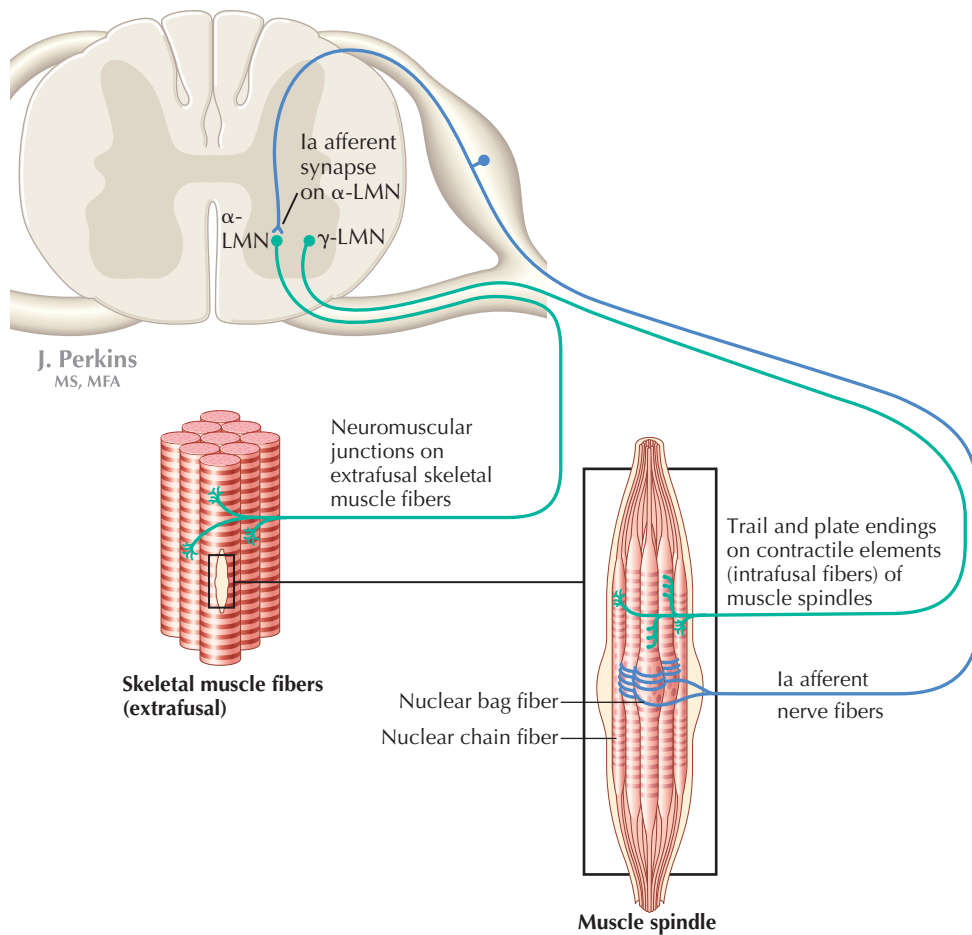
### Cerebellum

- 15.16 Functional Subdivisions of the Cerebellum
- 15.17 Cerebellar Neuronal Circuitry
- 15.18 Circuit Diagrams of Afferent Connections in the Cerebellum
- 15.19 Afferent Pathways to the Cerebellum
- 15.20 Cerebellar Efferent Pathways
- 15.21 Cerebellovestibular and Vestibulocerebellar Pathways
- 15.22 Schematic Diagrams of Efferent Pathways from the Cerebellum to Upper Motor Neuron Systems

### Basal Ganglia

- 15.23 Connections of the Basal Ganglia
- 15.24 Simplified Schematic of Basal Ganglia Circuitry and Neurochemistry
- 15.25 Parallel Loops of Circuitry through the Basal Ganglia
- 15.26 Connections of Nucleus Accumbens





## LOWER MOTOR NEURONS

### 15.1 ALPHA AND GAMMA LOWER MOTOR NEURONS

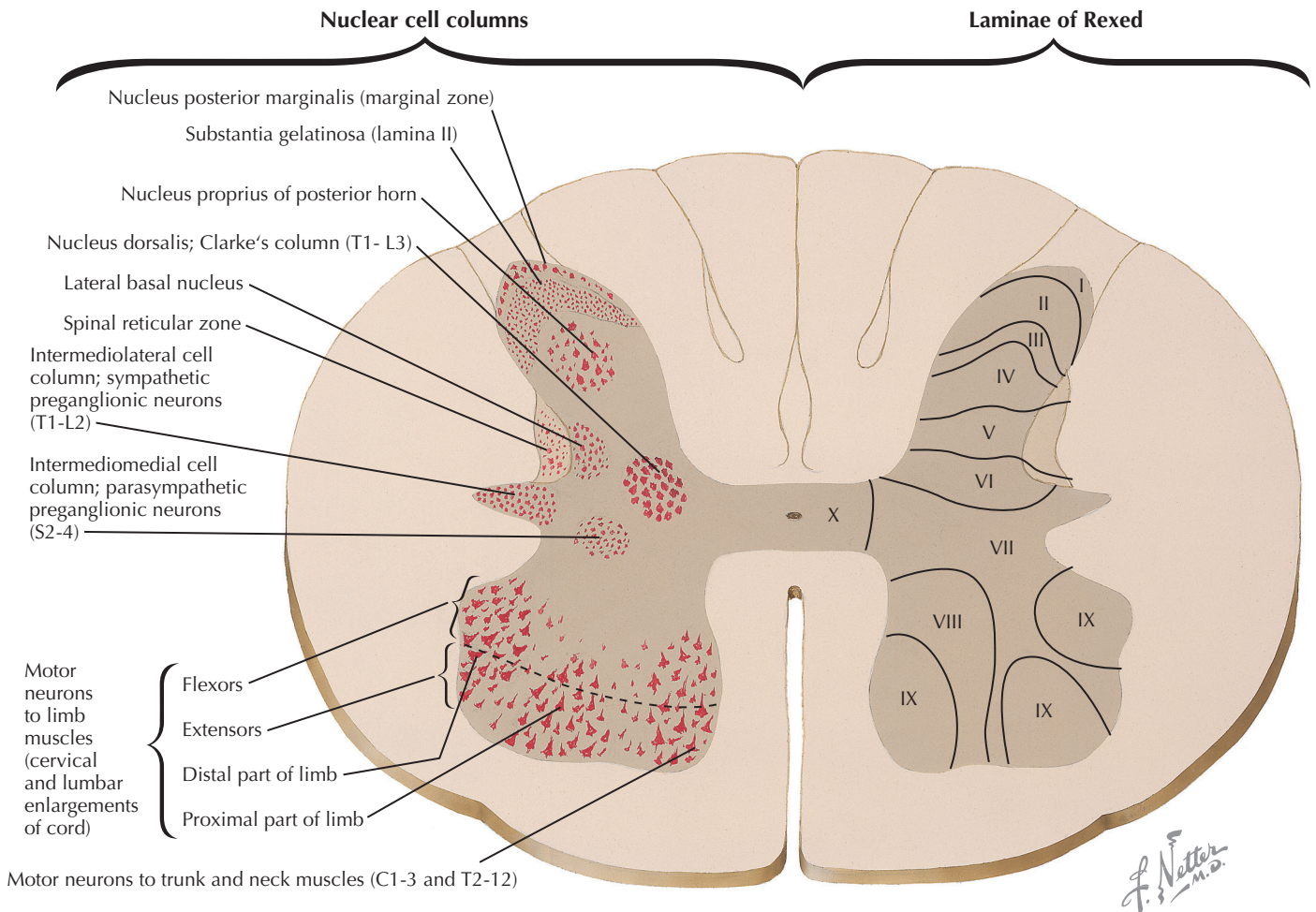
All lower motor neuron (LMN) groups except the facial nerve nucleus that supplies the muscles of facial expression consist of both alpha LMNs that supply the skeletal muscle fibers (extrafusal fibers) and gamma LMNs that supply the small contractile elements in the muscle spindles (intrafusal fibers). The muscles of facial expression do not have muscle spindles and are not supplied by gamma LMNs. The alpha LMNs regulate contraction of the skeletal muscles to produce movement. The gamma LMNs regulate the sensitivity of the muscle spindles for group Ia and group II afferent modulation of alpha LMN excitability.

#### CLINICAL POINT

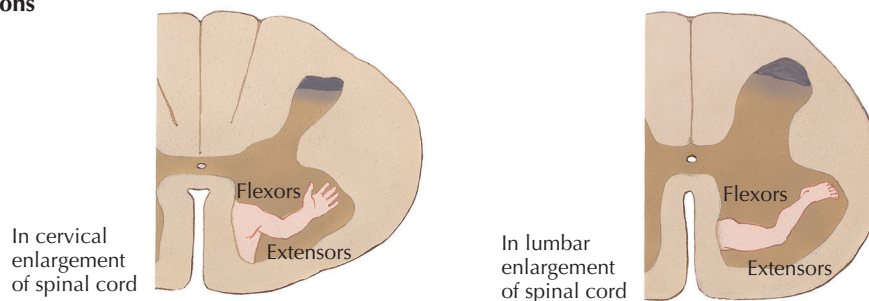
An alpha LMN supplies motor axons to a variable number of skeletal muscle fibers (extrafusal fibers), ranging from just a few (e.g., extraocular muscles) to several thousand (large muscles such as the quadriceps). The LMN and its innervated skeletal muscle fibers are called a motor unit. Supporting cells (such as Schwann cells) and myocytes produce trophic factors to maintain the nerve-muscle association; when nerve injury occurs, growth factors help to attract motor axonal regrowth to reestablish the prior nerve-muscle association. When

motor axons degenerate, the neuromuscular junctions (NMJs) disappear, and the nicotinic cholinergic receptors spread across the membrane of the denervated skeletal muscle fibers. This results in denervation hypersensitivity to nicotinic cholinergic stimulation, noted as random individual muscle fiber twitches (fibrillation), best observed by electromyography. If motor nerves are attracted back to the muscle fibers and NMJs are restored, the nicotinic cholinergic receptors are again restricted to the secondary folds of the NMJ. If the motor axon that was lost cannot regrow, neighboring motor axons of other motor units that supply adjacent skeletal muscle fibers may send sprouts to the denervated muscle fibers and incorporate them into the motor unit; the consequence is a larger motor unit and a greater demand on the LMN cell body that now supplies a greater than normal number of skeletal muscle fibers. This mechanism may account for recovery of physiological function in some LMN diseases such as polio. If the alpha-LMN cell body itself is damaged or is in the process of dying (e.g., in amyotrophic lateral sclerosis), the axon may produce aberrant action potentials (agonal bursts of electrical activity) that result in muscle fiber contraction throughout the motor unit, called a fasciculation, which is visually observable. A denervated muscle fiber must be reinnervated within 1 year or so if it is to restore relatively normal function; a longer period leads to permanent changes that preclude proper reinnervation. Many experimental approaches are seeking to restore innervation or attract a more robust nerve supply to denervated muscle fibers by applying or inducing gene expression of growth factors and trophic factors. Denervated skeletal muscle fibers are flaccidly paralyzed, lack muscle tone, cannot be induced to contract with muscle stretch reflexes, and undergo atrophy; these are classic characteristics of LMN syndrome.

### A. Cytoarchitecture of the spinal cord gray matter



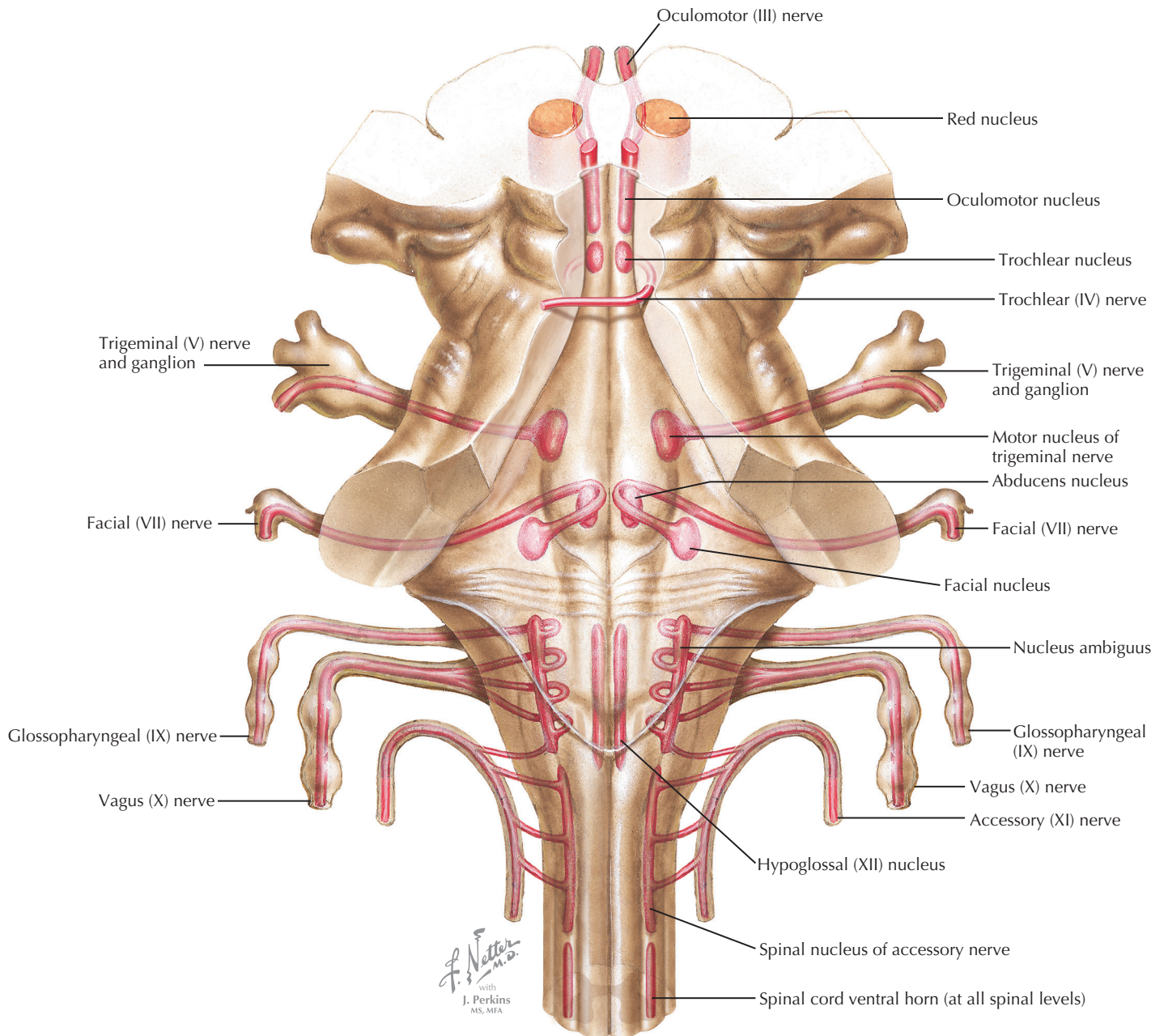
### B. Representation of motor neurons



## 15.2 DISTRIBUTION OF LOWER MOTOR NEURONS IN THE SPINAL CORD

LMNs are found as clusters of neurons in the anterior (ventral) horn of the spinal cord, represented as lamina IX of Rexed. Distinct clusters of LMNs supply distinct skeletal muscles with motor innervation. These LMN groups are organized topo-

graphically; LMNs distributing to trunk and neck muscles are found medially, and LMNs distributing to muscles of distal extremities are found laterally. Within spinal cord segments, LMNs distributing to flexor muscle groups are found dorsally, and LMNs distributing to extensor muscle groups are found ventrally.



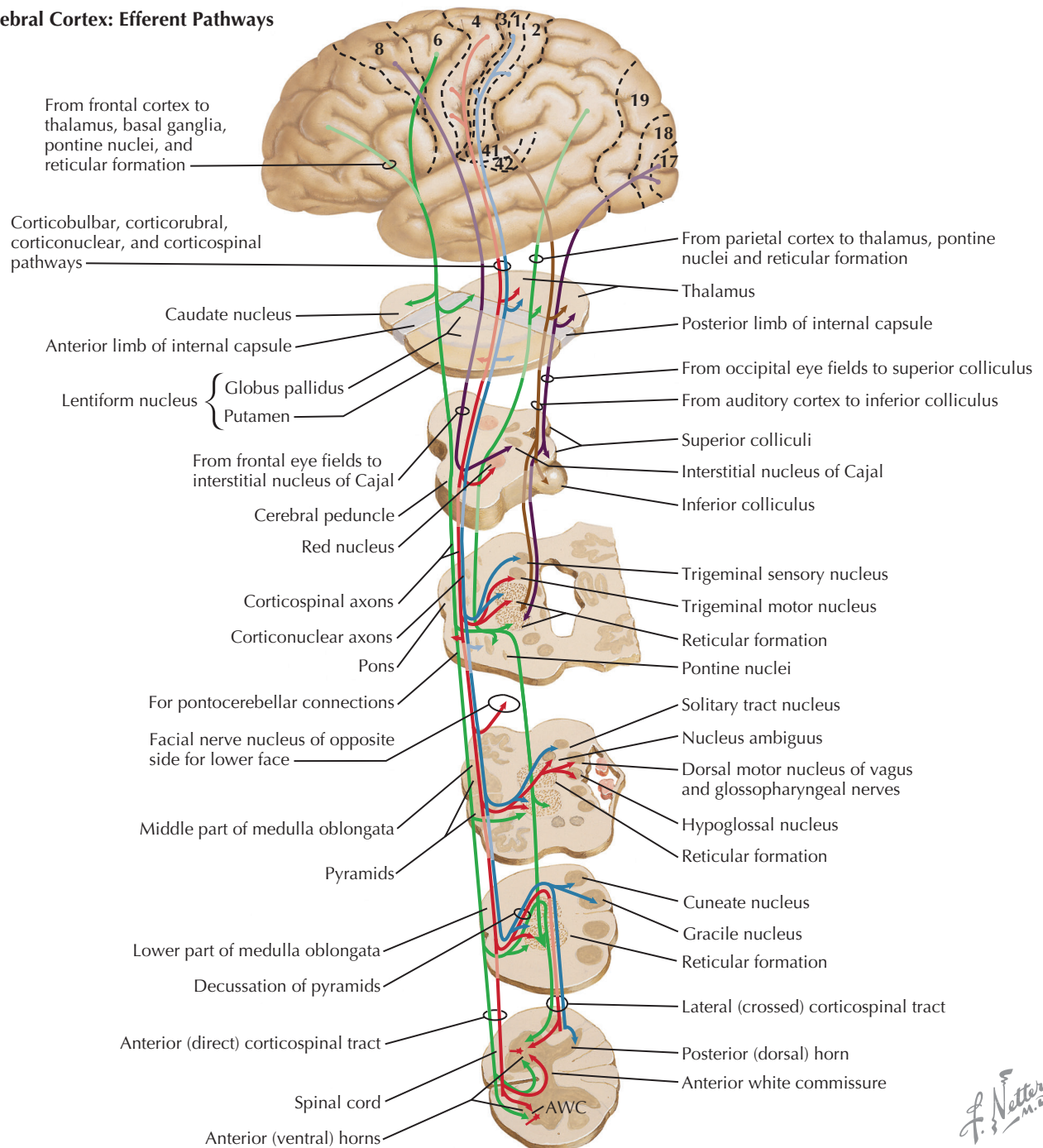
### 15.3 DISTRIBUTION OF LOWER MOTOR NEURONS IN THE BRAIN STEM

LMNs are found in medial and lateral columns in a longitudinal view of the brain stem. The medial column (LMNs of the oculomotor nucleus, trochlear nucleus, abducens nucleus, and hypoglossal nucleus) derives from the general somatic

efferent system, and the lateral column (LMNs of motor nucleus V, facial nucleus, nucleus ambiguus, and spinal accessory nucleus) derives from the special visceral efferent system. LMNs in the spinal cord are found in a longitudinal column coursing through the anterior horn at all levels.



## Cerebral Cortex: Efferent Pathways



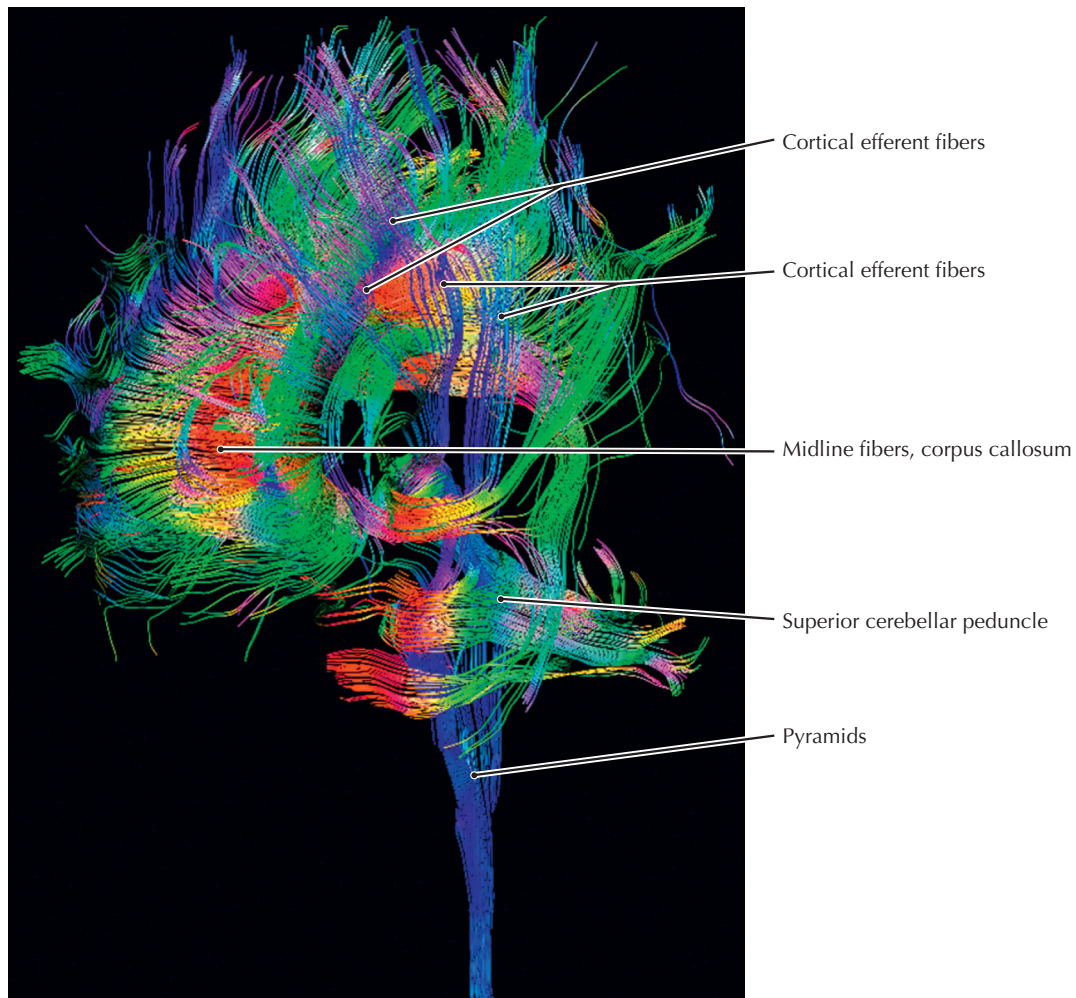
## UPPER MOTOR NEURONS

## 15.4 CORTICAL EFFERENT PATHWAYS

Cortical neurons in the motor cortex (area 4) and the supplementary and premotor cortices (area 6) send axons to the basal ganglia (caudate nucleus and putamen), the thalamus (ventral anterior [VA], and ventral lateral [VL] nuclei), the red nucleus, the pontine nuclei, the cranial nerve (CN) motor nuclei on both sides, and the spinal cord ventral horn, mainly on the contralateral side. These axons form the corticospinal tract, corticobulbar tract, corticostriatal projections, corticopontine projections, corticothalamic projections, and cortical connections to the upper motor neurons (UMNs) of the brain stem (reticular formation [RF] motor areas, red nucleus, superior

colliculus). Neurons of the sensory cortex (areas 3, 1, 2) send axons mainly to secondary sensory nuclei (corticonuclear fibers) to regulate incoming lemniscal sensory projections destined for conscious interpretation. Neurons in the frontal eye fields (area 8) project to the superior colliculus, the horizontal and vertical gaze centers of the brain stem, and the interstitial nucleus of Cajal to coordinate voluntary eye movements and associated head movements. Other regions of sensory cortex project axons to thalamic and brain stem structures that regulate incoming lemniscal sensory information. Some cortical efferent fibers project to limbic forebrain regions, such as the amygdaloid nuclei, hippocampal formation, and septal nuclei.

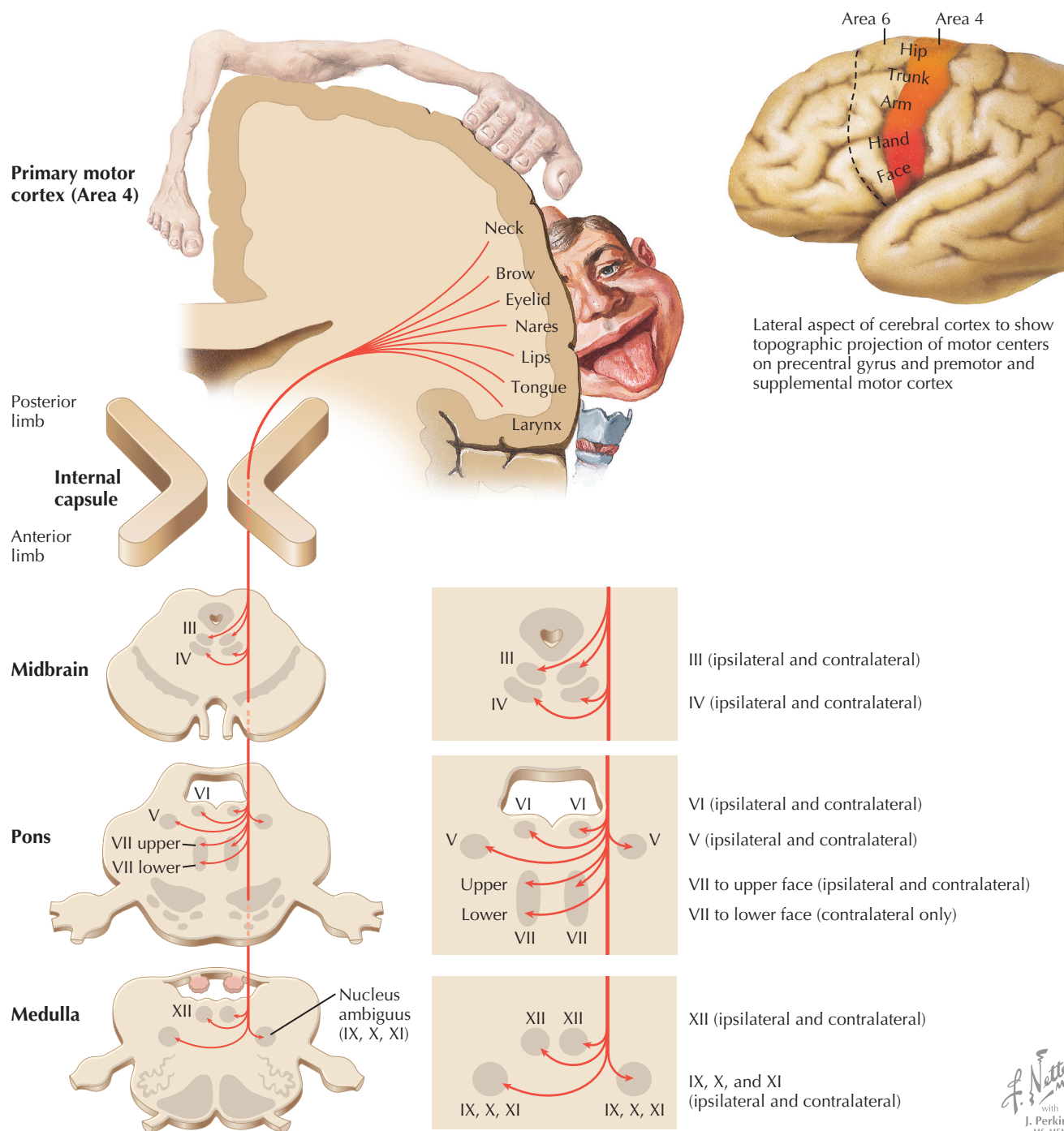
Lateral/oblique view



### 15.5 COLOR IMAGING OF CORTICAL EFFERENT PATHWAYS

This diffusion tensor image shows the cortical efferent pathways in a lateral oblique section. These pathways, shown in blue, channel from widespread areas of the cerebral cortex to structures in the forebrain, the thalamus, the brain stem, the

cerebellum (indirectly, through the pontine nuclei), and the spinal cord. Additional cortical association pathways are depicted in green (running in anterior-posterior direction) and commissural pathways are shown in red (running in left-right direction).



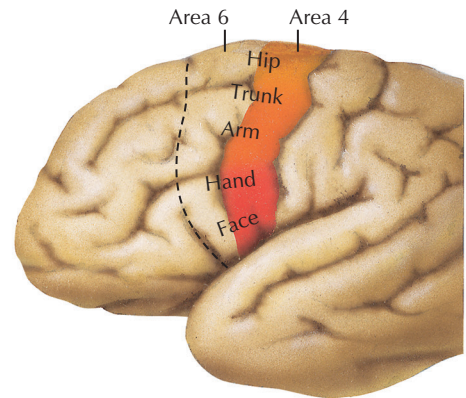
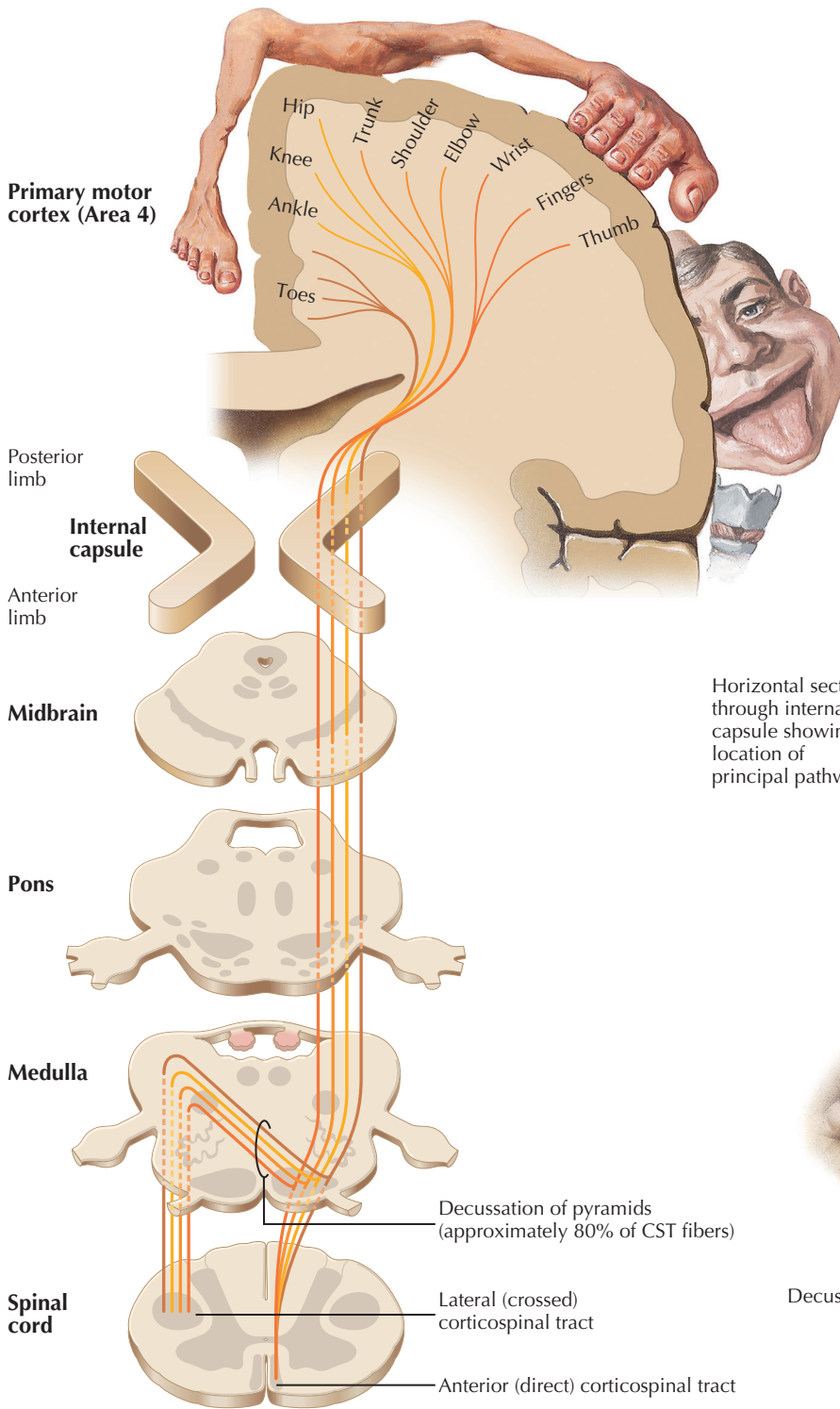
*f. Netter M.D.*  
with  
J. Perkins  
MS, MFA

### 15.6 CORTICOBULBAR TRACT

The corticobulbar tract (CBT) arises mainly from the lateral portion of the primary motor cortex (area 4). CBT axons project through the genu of the internal capsule into the cerebral peduncle, the basis pontis, and the medullary pyramids on the ipsilateral side. The axons distribute to CN motor nuclei on the ipsilateral and contralateral sides except for the portion of the facial nerve nucleus (CN VII) that supplies the

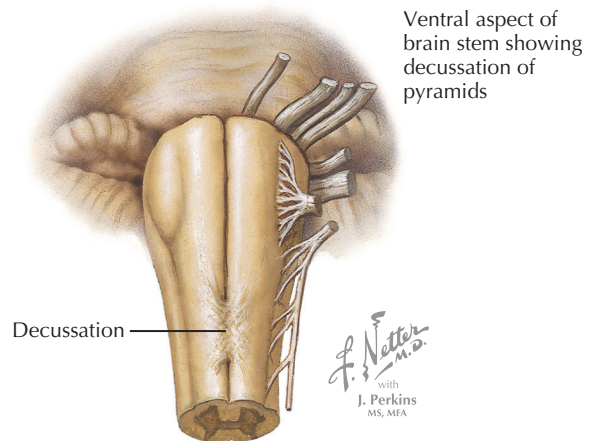
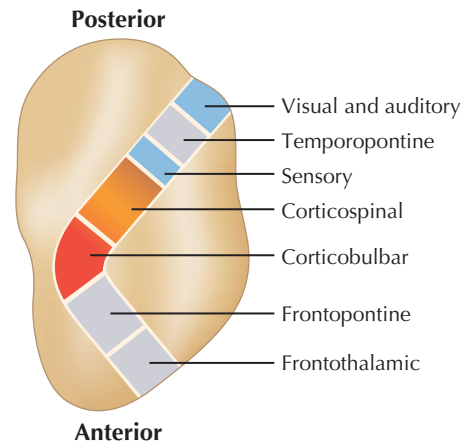
muscles of facial expression for the lower face, which receives exclusively contralateral projections. The CBT projections to the hypoglossal nucleus are mainly contralateral; CBT projections to the spinal accessory nucleus are mainly ipsilateral. CBT lesions result mainly in contralateral drooping lower face that is paretic to attempted movements from voluntary commands (central facial palsy), in contrast to Bell's palsy (CN VII palsy), in which the entire ipsilateral face is paralyzed.





Lateral aspect of cerebral cortex showing topographic localization of motor centers on precentral gyrus and premotor and supplemental motor cortex

Horizontal section through internal capsule showing location of principal pathways



## Corticospinal Tract

## 15.7 CORTICOSPINAL TRACT

The motor portion of the corticospinal tract (CST) originates from neurons of many sizes, mainly from the primary motor cortex (area 4) and the supplemental and premotor cortices (area 6). The primary sensory cortex (areas 3, 1, 2) contributes axons into the CST, but these axons terminate mainly in secondary sensory nuclei to regulate the processing of incoming lemniscal sensory information. The CST travels through the posterior limb of the internal capsule, the middle region of the cerebral peduncle, numerous fascicles of axons in the basis pontis, and the medullary pyramid on the ipsilateral side. Most of the CST axons (approximately 80%, but variable from individual to individual) cross the midline in the decussation of the pyramids at the medullary-spinal cord junction. These crossed fibers descend in the lateral CST in the lateral funiculus of the spinal cord and synapse on alpha and gamma LMNs, both directly and indirectly through interneurons. CST axons that do not decussate continue as the anterior CST in the anterior funiculus of the spinal cord and then decussate at the appropriate level through the anterior white commissure to terminate directly and indirectly on alpha and gamma LMNs contralateral to the cortical cells of origin. Only a very small portion of the motor connections of the corticospinal tract terminate on LMNs on the ipsilateral side of the spinal cord.

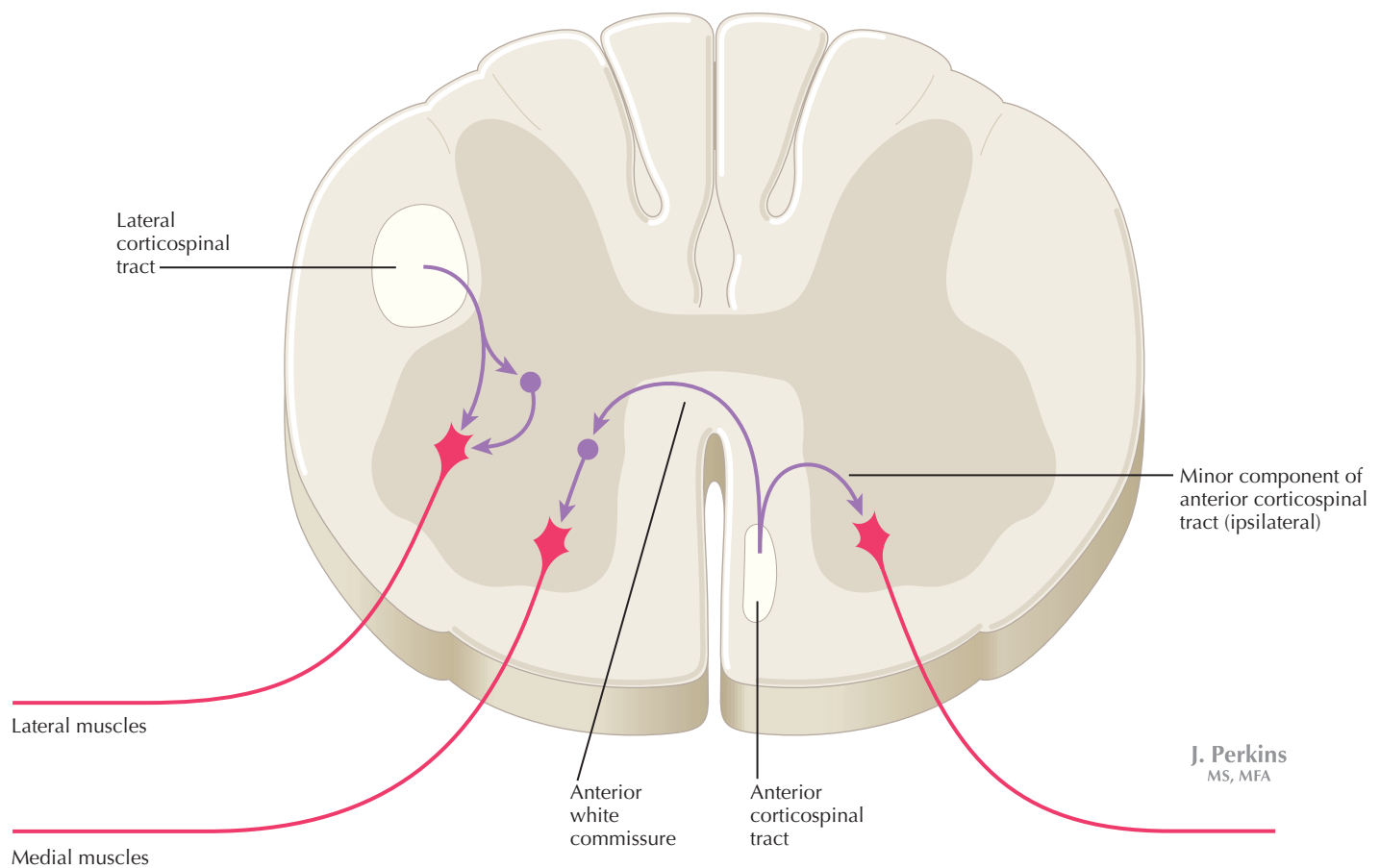
### CLINICAL POINT

The motor portion of the CST arises mainly from neurons in the primary motor cortex (area 4) and the supplemental and premotor cortices (area 6). The primary sensory cortex and superior parietal lobule contribute corticospinal axons (corticonuclear fibers) to secondary sensory nuclei in the lower brain stem and spinal cord. Approximately 80% of the CST axons cross in the decussation of the pyramids and terminate directly and indirectly with alpha and gamma LMNs that control movements of the distal extremities, especially the hands and fingers. At least 10% of the CST terminates monosynaptically on alpha LMNs, especially those associated with hand and finger musculature. A lesion in the internal capsule damages the CST, corticobulbar fibers, and corticoreticular fibers, resulting in contralateral hemiplegia. Initially, the hemiplegia is flaccid, with loss of tone and reflexes. Within days to a week or so, the hemiplegia becomes spastic, with hyperreflexia and hypertonus. The affected musculature shows initial resistance to attempted passive movement, followed by a dissipation or “melting” of tone (the clasp-knife reflex), perhaps because

of high threshold Ib Golgi tendon organ inhibitory influences on the homonymous LMNs. The initial suspected mechanism of classical UMN syndrome was disinhibition of dynamic gamma LMNs, which drives initial resistance to passive stretch, mediated via subsequent Ia afferent influences over alpha LMNs; this mechanism was reinforced by observations that dorsal root sectioning diminished spasticity in UMN syndromes. Further studies have revealed additional potential mechanisms, including diminished reciprocal inhibition, recurrent Renshaw inhibition, and presynaptic inhibition on Ia afferents, all suggestive of major changes in interneurons of the spinal cord following a classic UMN lesion. In UMN syndrome, the plantar reflexes are extensor (reverting to a developmentally early stage in the absence of the CST), and abdominal reflexes are absent on the affected side. Clonus (repetitive alternating flexor and extensor muscle stretch reflexes) also may occur and is possibly attributable to interneuronal changes such as diminished Renshaw inhibition.

### CLINICAL POINT

The CBT arises mainly from the lateral portion of the primary motor cortex; it descends through the genu of the internal capsule and the cerebral peduncle (medial to the corticospinal tract fibers) ipsilaterally, and it distributes bilaterally to the motor CN nuclei (CNN) of the brain stem, except to the facial nucleus for the lower face, which receives almost exclusively contralateral projections. The corticobulbar axons terminate mainly on interneurons that regulate LMN output. Originally, *corticobulbar* was a term reserved for cortical projections to LMNs of the medulla (bulb), but it now has been expanded to include CNN for V, VII, nucleus ambiguus, XII, and the spinal accessory (XI) nucleus. A lesion in the genu of the internal capsule (embolic or thrombotic stroke, or hemorrhage of the middle cerebral artery or its branches) or the cerebral peduncle (Weber's syndrome, compression of the peduncle against the free edge of the tentorium cerebelli with transtentorial herniation) results mainly in a drooping lower face (central facial palsy) on the contralateral side. The intact hemisphere can control voluntary movement of the LMNs in the CNN for all other brain stem motor nuclei on both sides. In some individuals, a predominance of contralateral fibers to LMNs for the soft palate or the tongue is noted, resulting in a temporary contralateral palsy; or a predominance of ipsilateral fibers to LMNs of XI may be noted, resulting in an ipsilateral palsy of the sternocleidomastoid and upper trapezius muscles. This central paresis occurs without atrophy. Bilateral corticobulbar lesions result in profound paralysis of voluntary movement in all muscles supplied by CNN, with preservation of muscle bulk, reflex responses, and some emotional responses using those LMNs. The LMNs in CNN III, IV, and VI receive cortical input from the frontal eye fields (area 8) and parietal eye fields of both sides.

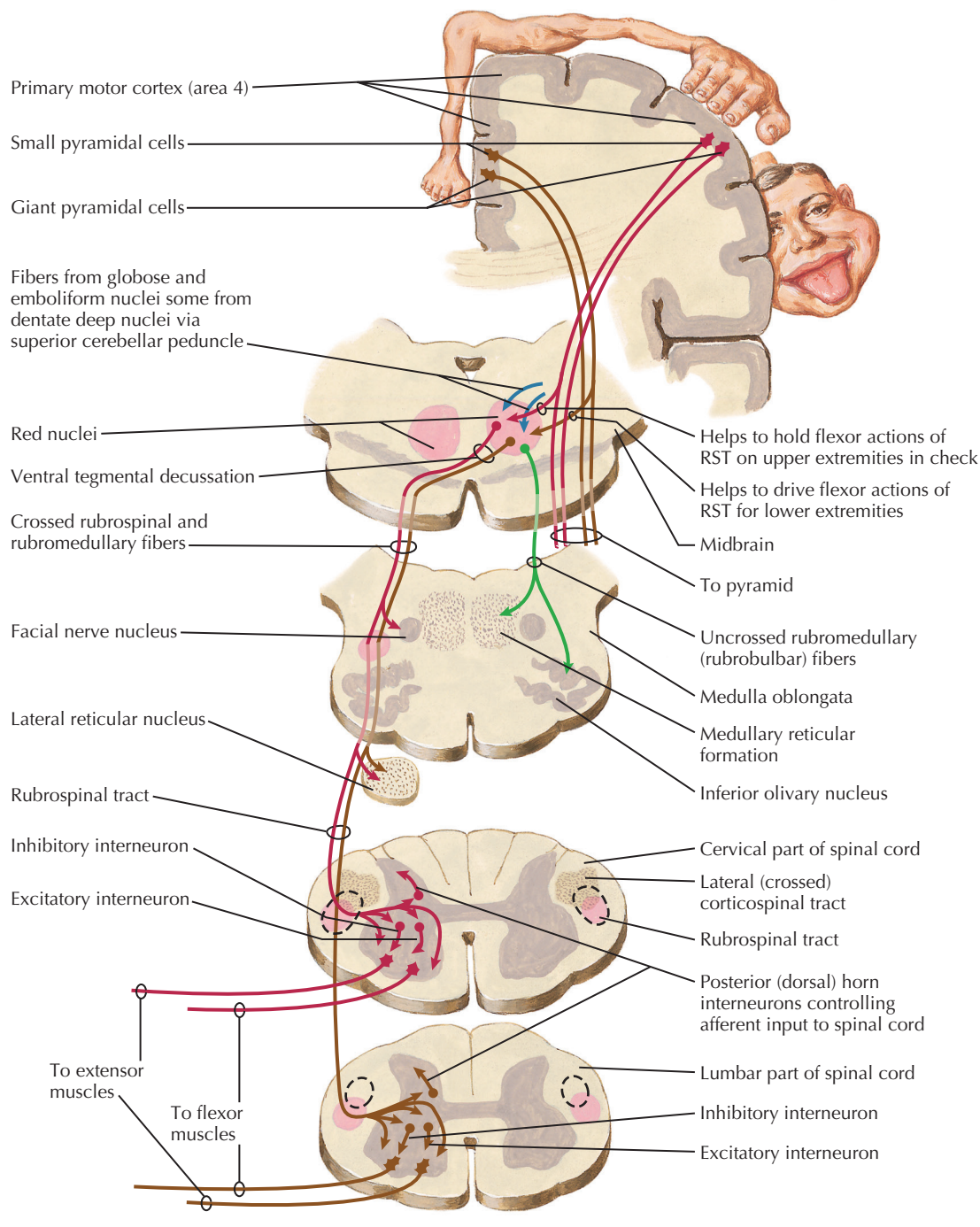


### 15.8 CORTICOSPINAL TRACT TERMINATIONS IN THE SPINAL CORD

Crossed axons in the lateral CST, intermixed with axons of the rubrospinal tract, travel in the lateral funiculus. These CST axons terminate directly and indirectly mainly on LMNs associated with distal musculature, especially for skilled hand and finger movements. The uncrossed anterior CST axons decussate predominantly in the anterior white commissure and terminate directly and indirectly mainly on LMNs that supply medial musculature. A small number of anterior CST axons terminate ipsilateral to the cortical cells of origin. An isolated

lesion in the CST in the medullary pyramids results in weakness of contralateral fine, dexterous hand and finger movements. All other lesions involving the CST at other levels (internal capsule, cerebral peduncle, pons), where these descending fibers are intermixed with other descending motor systems, produce contralateral spastic hemiplegia with hypertonus, hyperreflexia, and plantar extensor responses as long-term consequences. Lesions in the lateral CST produce similar symptoms ipsilateral to the damaged lateral funiculus below the level of the lesion.



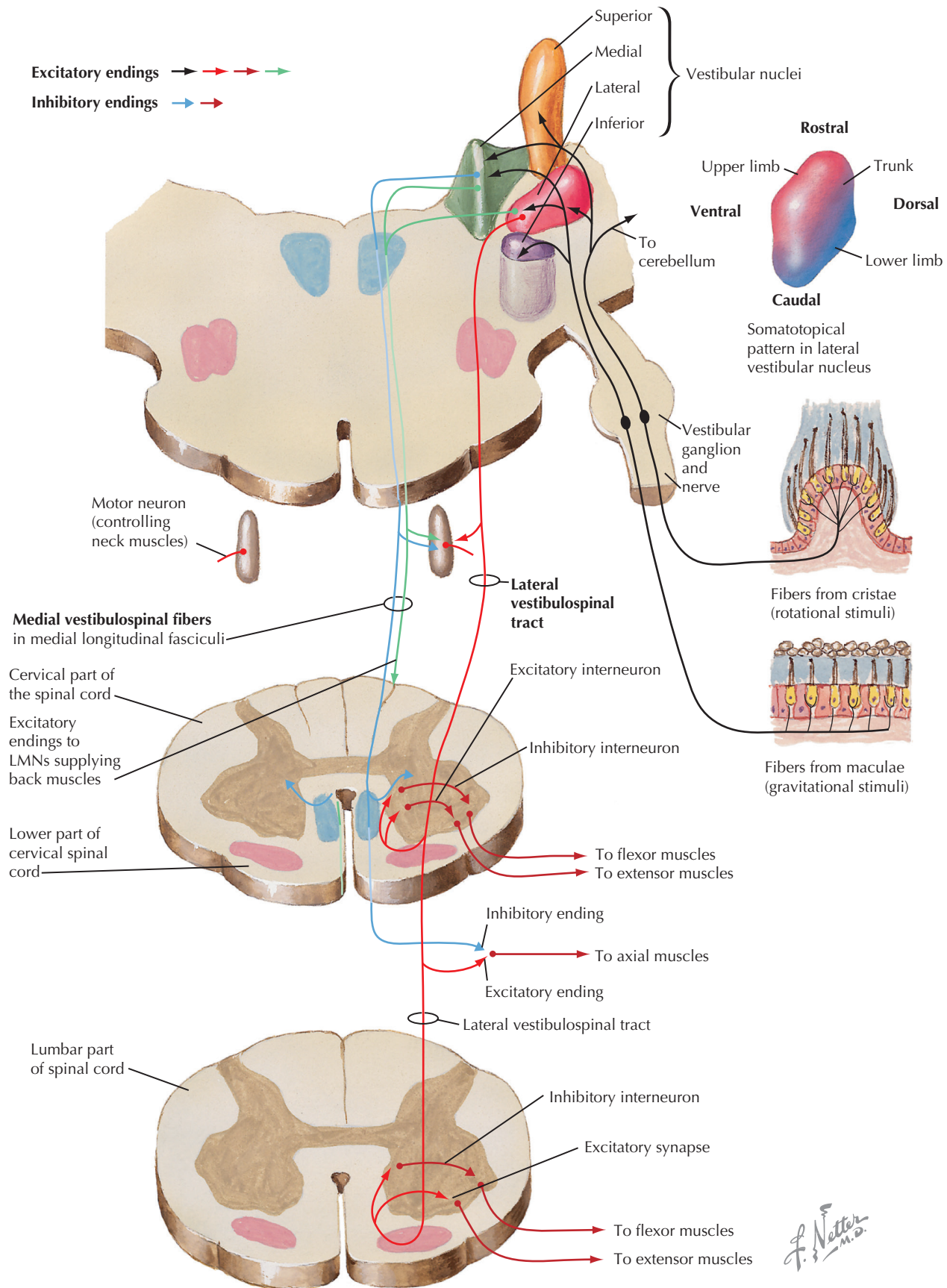


*F. Netter M.D.*

### 15.9 RUBROSPINAL TRACT

The cortico-rubro-spinal system is an indirect corticospinal system that regulates spinal cord LMNs. The red nucleus in the midbrain receives topographically organized ipsilateral connections from the primary motor cortex (area 4). Axons of the rubrospinal tract (RST) decussate in the ventral tegmental decussation and descend in the lateral brain stem and the lateral funiculus of the spinal cord, where they are intermixed extensively with axons of the lateral CST. The RST terminates directly and indirectly on alpha and gamma LMNs in the spinal cord, particularly those associated with flexor

movements of the extremities. The RST helps to drive flexor movements of the upper extremity and helps to hold in check flexor movements of the lower extremity. RST lesions usually occur in conjunction with the CST in the spinal cord; corticorubral lesions also occur in conjunction with the CST in the internal capsule and cerebral peduncle. These lesions result in contralateral spastic hemiplegia as long-term consequences. Brain stem lesions caudal to the red nucleus result in decerebration (extensor spasticity), reflecting the removal of the flexor drive of the rubrospinal tract to LMNs supplying the upper limbs. See page 420 for a Clinical Point.



*F. Netter M.D.*

**Vestibulospinal Tracts**

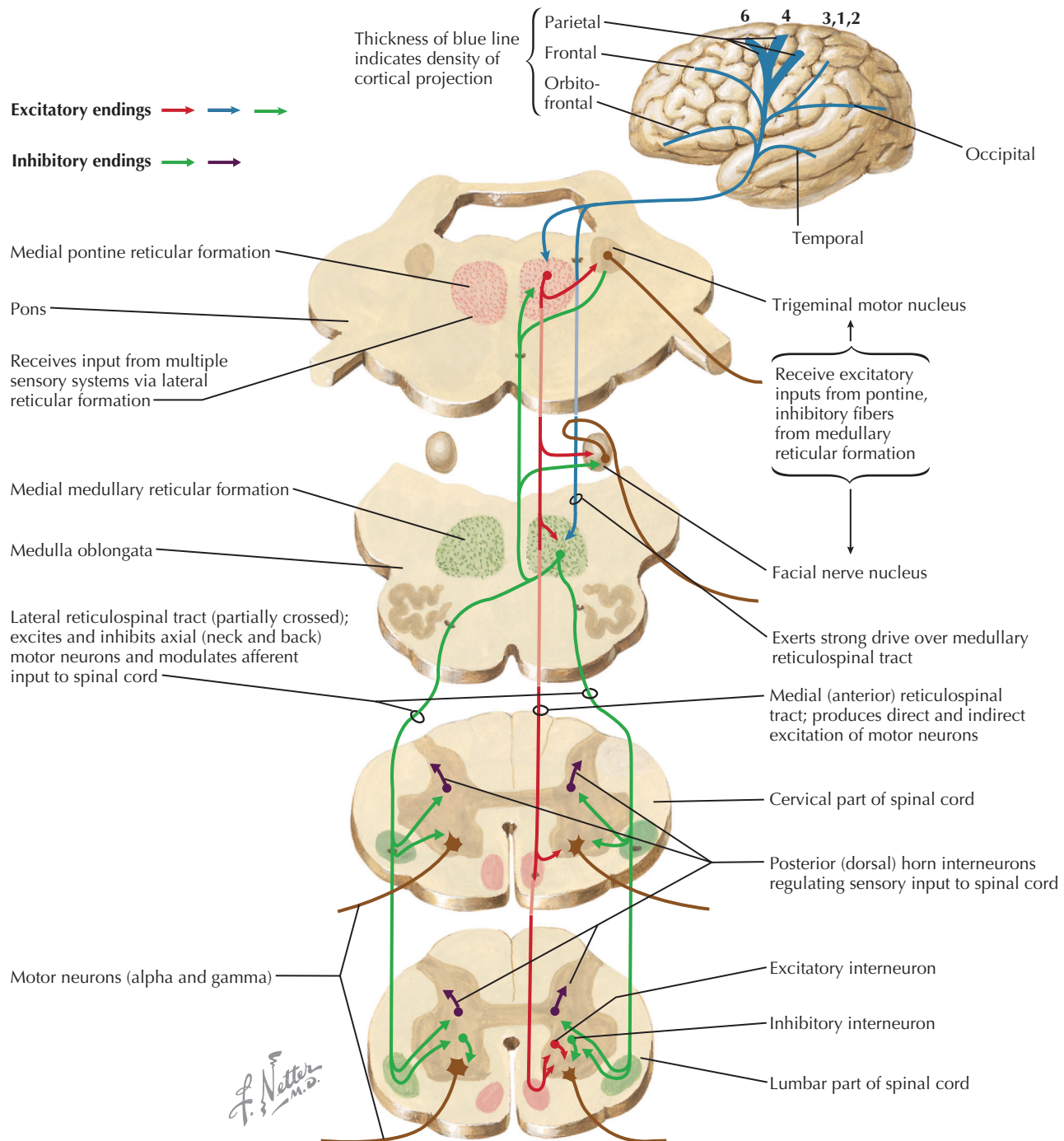
### 15.10 VESTIBULOSPINAL TRACTS

The lateral vestibulospinal tract arises from the lateral vestibular nucleus and terminates directly and mainly indirectly on ipsilateral alpha- and gamma-LMNs associated with extensor musculature, especially proximal musculature. If this powerful antigravity extensor system were not kept in check by descending connections from the red nucleus and by connections from the cerebellum, it would produce a constant state of extensor hypertonus. Removal of these influences can occur with lesions caudal to the red nucleus, producing decerebration with powerful extensor posturing. The medial vestibulospinal tract arises from the medial vestibular nucleus and provides inhibition of alpha- and gamma-LMNs controlling neck and axial musculature. The medial vestibulospinal tract terminates mainly on interneurons in the cervical spinal cord ventral horn. These two vestibulospinal tracts stabilize and coordinate the position of the head, neck, and body and provide important reflex and brain stem control over tone and posture. The vestibulospinal tracts work with the reticulospinal tracts to control tone and posture.

#### CLINICAL POINT

Primary vestibular input from both the maculae of the utricle and the cristae of the ampullae of the semicircular canals terminates in the vestibular nuclei of the medulla and pons, including the cells of origin of the vestibular UMN tracts, the lateral and medial vestibular nuclei. This allows influences from the direction of the gravitational field (linear acceleration) and head movement (angular acceleration) to affect the firing of neurons in the vestibular nuclei. The lateral vestibular nuclei give rise to a powerful vestibulospinal antigravity system that terminates mainly indirectly on alpha- and gamma-LMNs in the medial part of the ventral horn, which is associated with proximal extensor musculature. This system, if left unchecked and uninhibited, would drive the neck and body into marked extensor posturing, called decerebration (or decerebrate rigidity). The lateral vestibulospinal system is inhibited mainly by the red nucleus and the anterior cerebellum. In decerebrate posturing, sectioning of the dorsal roots (dorsal rhizotomy) abolishes the extraordinary “rigidity” (it is actually spasticity, not true rigidity), suggesting the decerebration results from the unregulated activity of the reticulospinal and lateral vestibulospinal tract driving the gamma-LMNs. This is consistent with the earlier hypothesis of the mechanism of spasticity, although additional spinal interneuronal inhibition is also most likely involved in decerebrate posturing. The medial vestibulospinal tract exerts inhibitory influences on LMNs that innervate neck muscles, permitting unconscious adjustments to move the head in response to vestibular stimuli. Thus, the vestibulospinal tracts help to promote body and head movements to maintain appropriate posture with vestibular activation, particularly during movement; these systems also coordinate with projections via the medial longitudinal fasciculus that synchronize eye movements.

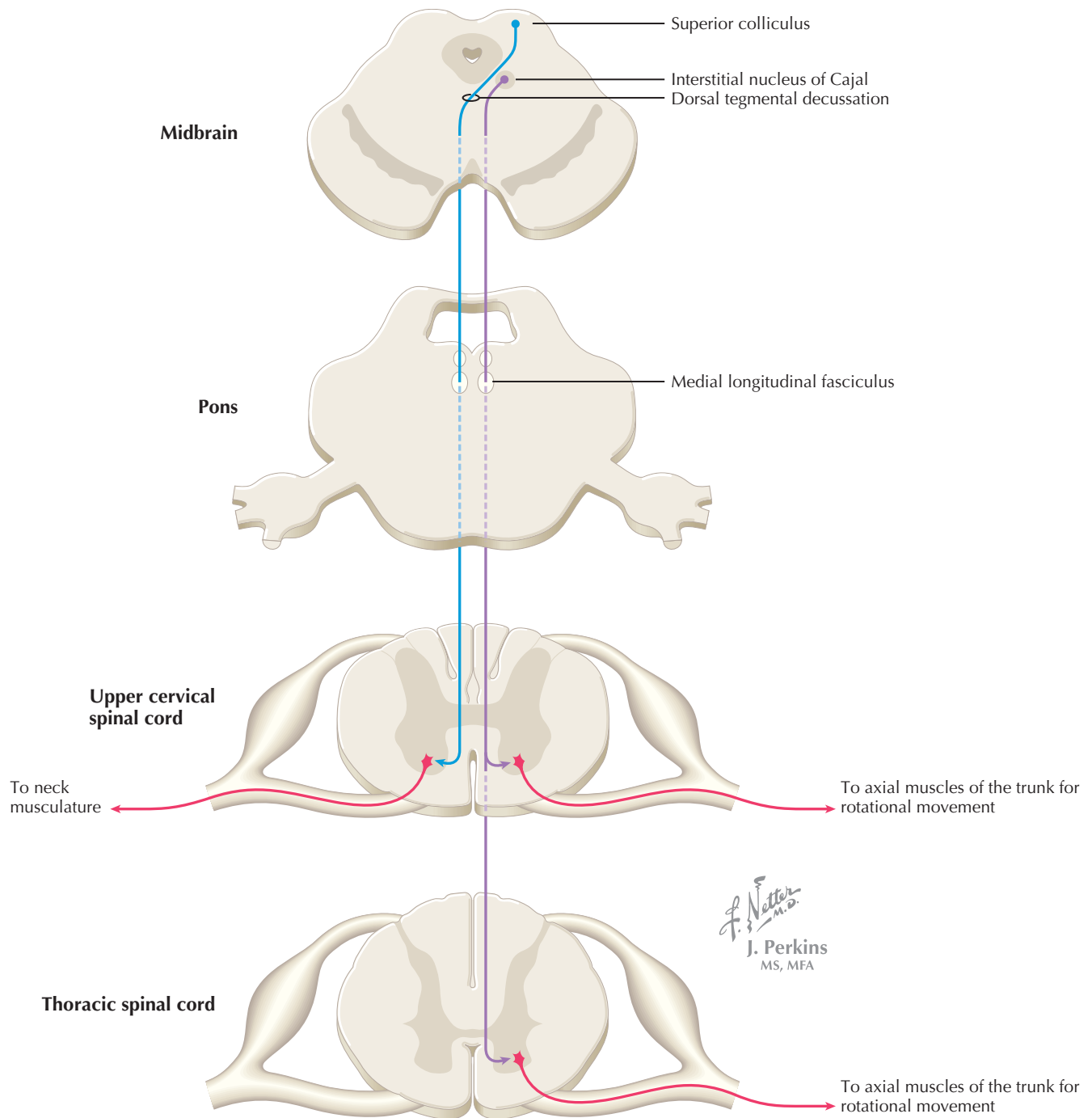




### 15.11 RETICULOSPINAL AND CORTICORETICULAR PATHWAYS

The pontine reticulospinal tract (RetST) arises from neurons of the medial pontine RF (nuclei pontis caudalis and oralis). Axons descend as the pontine (medial) RetST, mainly ipsilaterally, and terminate directly and indirectly on alpha- and gamma-LMNs at all levels. This tract has a distinct extensor bias for axial musculature and reinforces the action of the lateral vestibulospinal tract. Although some cortical axons terminate in the nuclei of origin of the pontine RetST, the cortex provides minimal influence on the activity of this tract; the

pontine RetST is driven primarily by polysensory input from trigeminal and somatosensory sources. The medullary RetST originates from the medial RF (nucleus gigantocellularis) and is heavily driven by cortical input, especially from the motor cortex and supplemental and premotor cortices. Axons of the medullary (lateral) RetST terminate bilaterally, directly and indirectly, on alpha- and gamma-LMNs at all levels. The medullary RetST exerts a flexor bias, reinforcing the CST and RST. The reticulospinal tracts are important regulators of basic tone and posture. They are not organized somatotopically. See page 420 for a Clinical Point.



### 15.12 TECTOSPINAL TRACT AND INTERSTITIOSPINAL TRACT

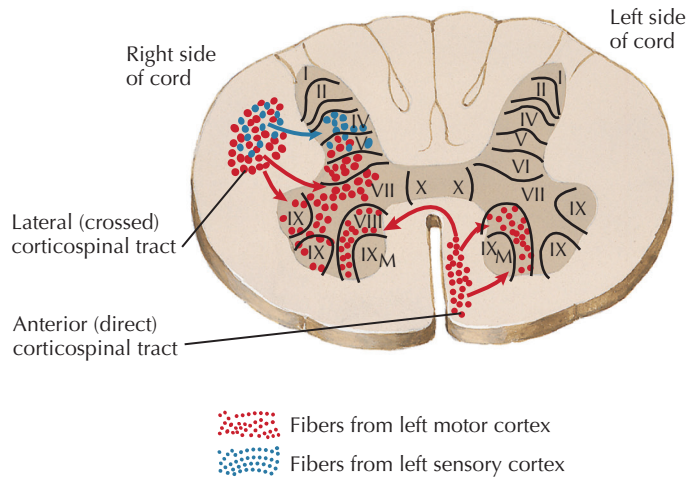
The tectospinal tract arises from neurons in deep layers of the superior colliculus, decussates in the dorsal tegmental decussation, descends contralaterally near the midline, and terminates directly and indirectly on alpha- and gamma-LMNs in the cervical spinal cord associated with head and neck movements. This pathway mediates reflex and visual tracking influences for positioning the head with regard to visual input. The interstitiospinal tract arises from the interstitial nucleus of Cajal, a region of the midbrain that helps to coordinate eye movements and gaze centers. The interstitiospinal tract descends ipsilaterally in the medial longitudinal fasciculus and

terminates directly and indirectly on alpha- and gamma-LMNs associated with the axial musculature of the trunk that is involved in rotational movement of the body around its central axis.

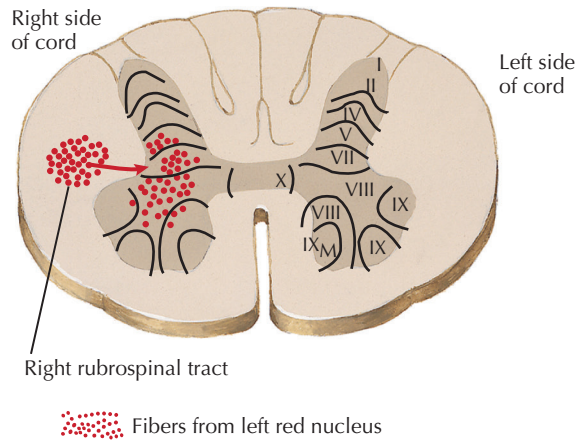
#### CLINICAL POINT

The superior colliculus, neurons of origin of the tectospinal tract, is responsive to input from the retina, the visual cortex, and the frontal eye fields. Of particular note is the role of tectospinal and tectobulbar projections (especially to the reticular formation) that help to coordinate movements of both the head and the eyes. Part of the tectospinal pathway may receive indirect input from the inferior colliculus and help to mediate head movements in response to loud or conspicuous sounds.

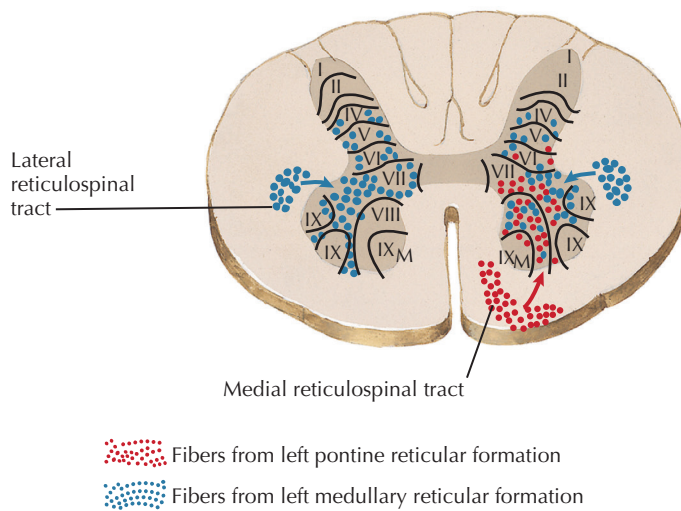
### A. Corticospinal tracts



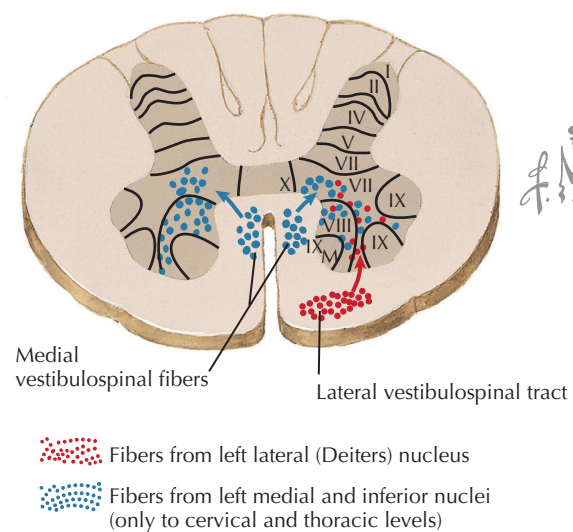
### B. Rubrospinal tracts



### C. Reticulospinal tracts



### D. Vestibulospinal tracts

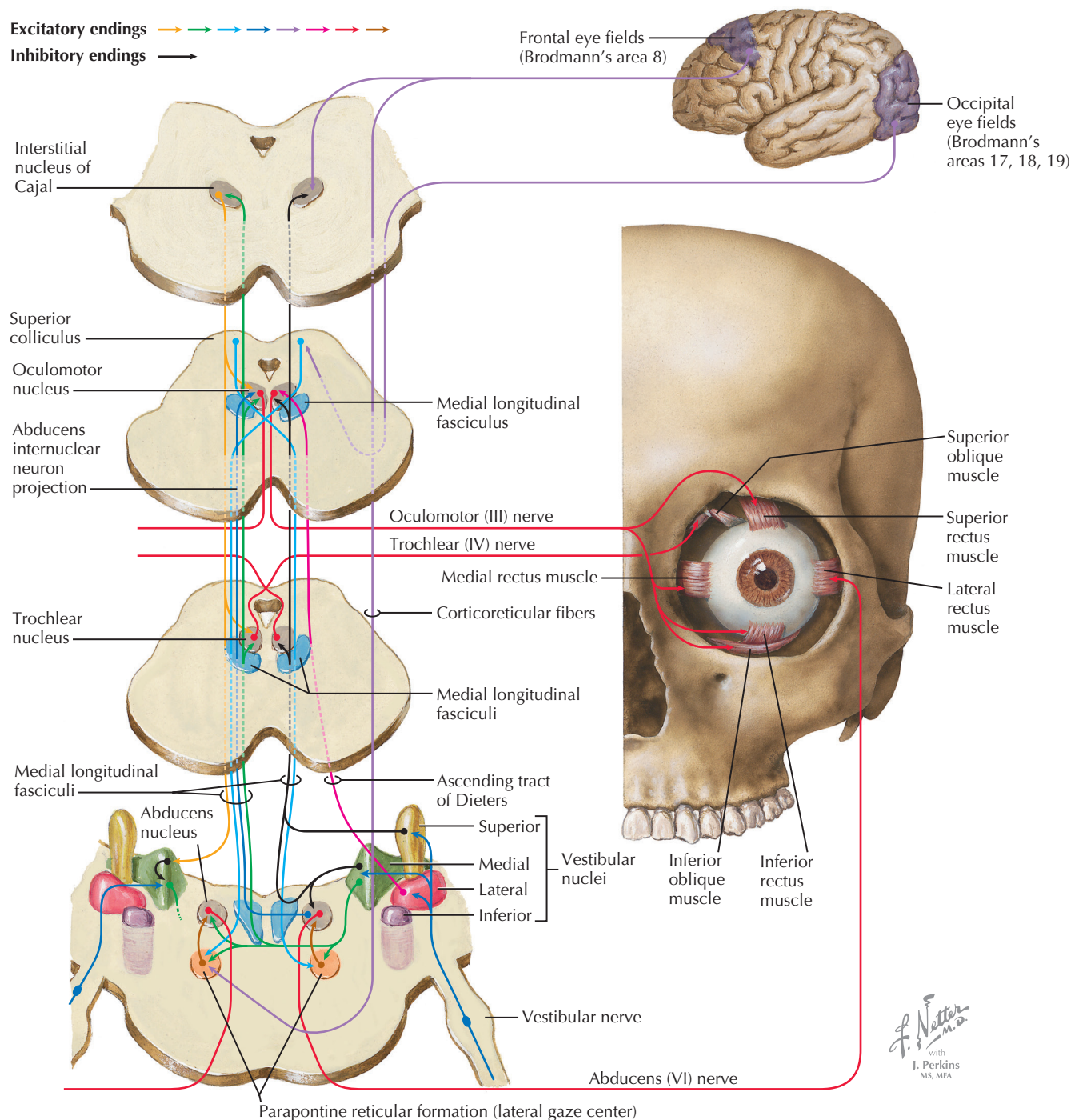


## 15.13 SPINAL CORD TERMINATIONS OF MAJOR DESCENDING UPPER MOTOR NEURON TRACTS

The lateral corticospinal tract and the rubrospinal tract terminations are directed mainly toward LMNs associated with

distal limb musculature. The anterior CST, the reticulospinal tracts, and the vestibulospinal tracts are directed mainly toward LMNs associated with more proximal and axial musculature.

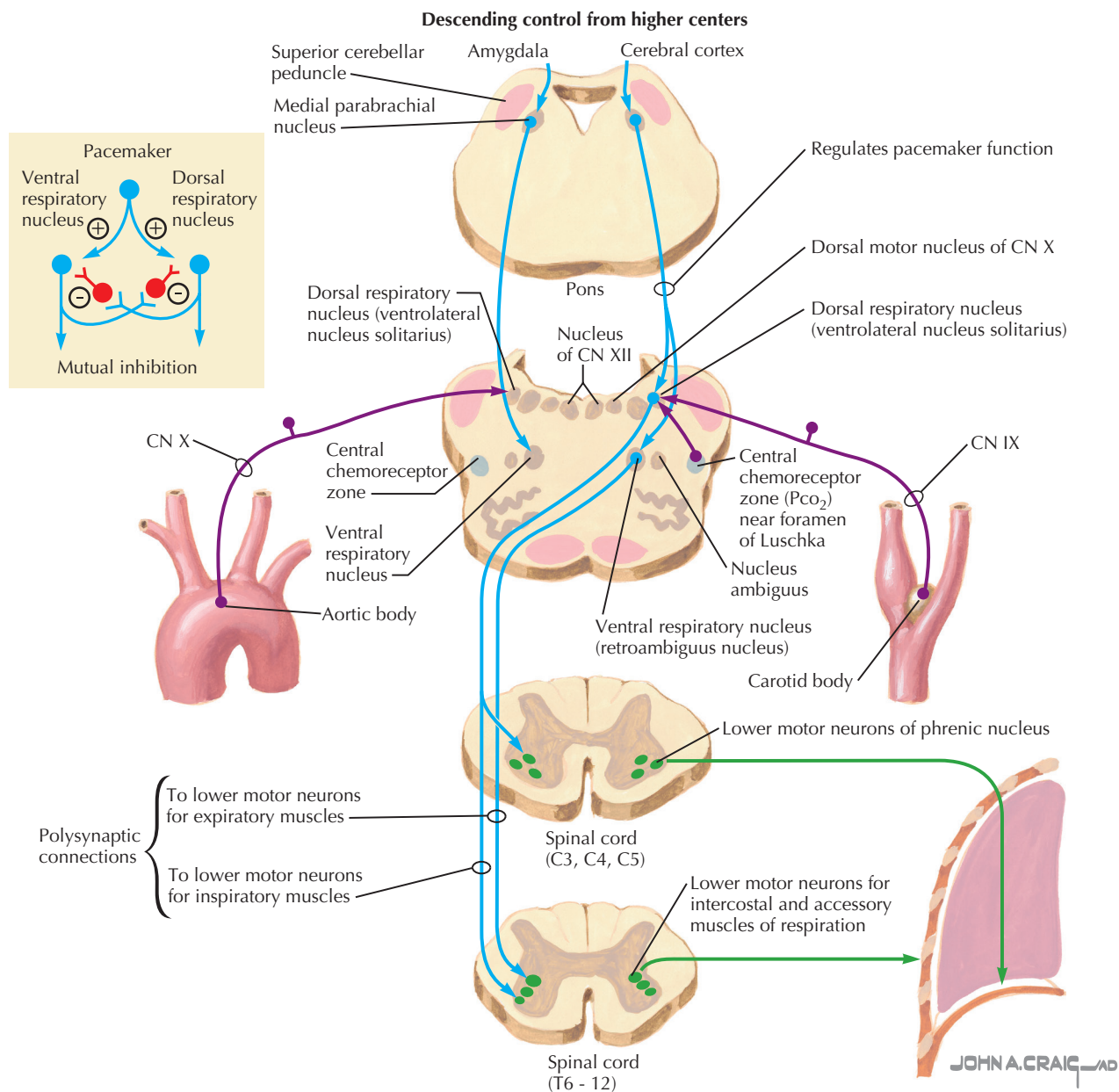




### 15.14 CENTRAL CONTROL OF EYE MOVEMENTS

Central control of eye movements is achieved through the coordination of extraocular motor nuclei for CNs III (oculomotor), IV (trochlear), and VI (abducens). This is achieved by the parapontine reticular formation (horizontal gaze center); it receives input from the vestibular nuclei; the deep layers of the superior colliculus (input from V1, V2, and V3); the cerebral cortex (frontal eye fields); and the interstitial nucleus of Cajal (which receives input from the vestibular nuclei and the frontal eye fields). The parapontine reticular formation sup-

plies the ipsilateral VI nucleus for movement of the lateral rectus muscle and the contralateral III nucleus (via interneurons in VI nucleus) for movement of the medial rectus muscle, thus coordinating horizontal eye movements. The interstitial nucleus of Cajal helps to coordinate vertical and oblique eye movements. Secondary sensory vestibular projections also terminate in the extraocular motor CNN. Axons interconnecting the extraocular motor CNN travel through the medial longitudinal fasciculus. See page 420 for a Clinical Point.

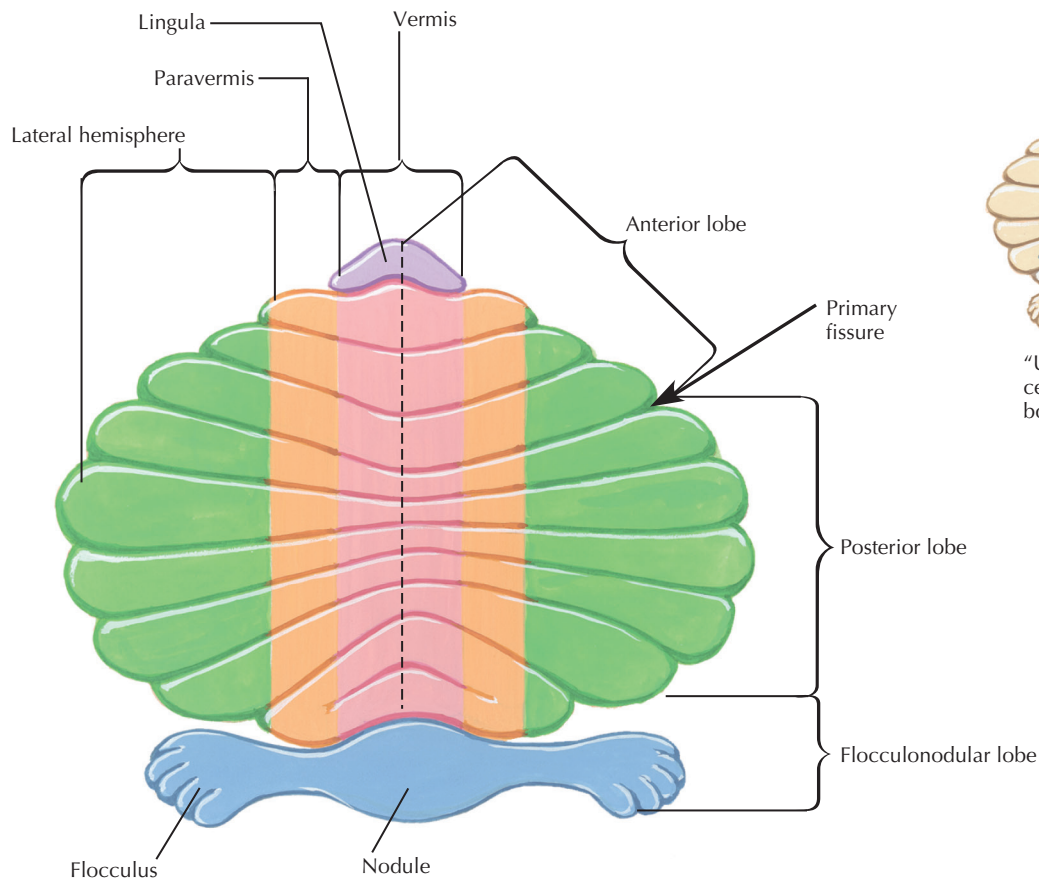


### 15.15 CENTRAL CONTROL OF RESPIRATION

Inspiration and expiration are regulated by nuclei of the reticular formation (RF). The dorsal respiratory nucleus (lateral nucleus solitarius) sends crossed axons to terminate on cervical spinal cord LMNs of the phrenic nucleus and on thoracic spinal cord LMNs that supply intercostal muscles and accessory musculature associated with inspiration. The ventral respiratory nucleus (nucleus retroambiguus) sends crossed axons to terminate on thoracic spinal cord LMNs that supply accessory musculature associated with expiration. The dorsal respiratory nucleus receives input from the carotid body (via CN IX); from the aortic body chemosensors (via CN X); and from central chemoreceptive zones of the lateral medulla. The dorsal respiratory nucleus and ventral respiratory nucleus mutually inhibit each other. The medial parabrachial nucleus acts as a respiratory pacemaker to regulate the dorsal respiratory nucleus and the ventral respiratory nucleus. The medial parabrachial nucleus receives input from higher centers, such as the amygdala and the cerebral cortex.

#### CLINICAL POINT

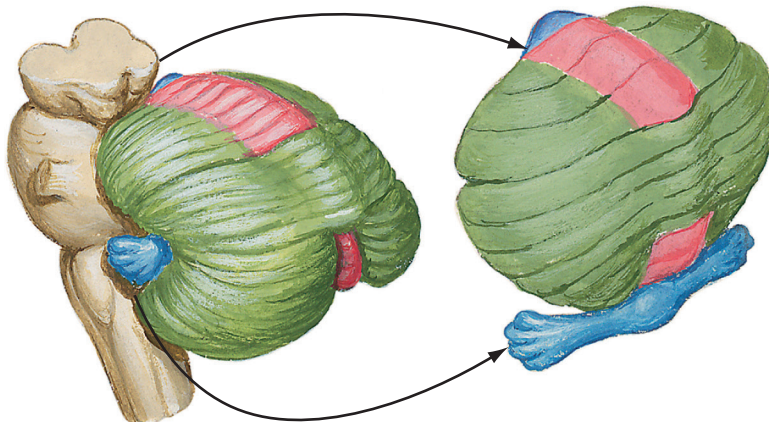
The dorsal respiratory nucleus (lateral nucleus solitarius) sends axonal projections to the contralateral cervical LMNs of the phrenic nucleus and thoracic LMNs of accessory respiratory muscles, regulating inspiration. The ventral respiratory nucleus (nucleus retroambiguus) sends axonal projections to contralateral thoracic LMNs that supply accessory musculature associated with expiration. The medial parabrachial nucleus functions as a pacemaker and receives input from higher levels of the central nervous system. Progressive damage to the forebrain and brain stem elicits relatively predictable changes in respiration. Progressive damage through the telencephalon and diencephalons elicits Cheyne-Stokes respiration (crescendo-decrescendo breathing; periods of hyperpnea alternating with brief periods of apnea). The hyperpnea phase is provoked by  $P_{CO_2}$  from the apneic phase and results in the lowering of  $P_{CO_2}$ , again provoking apnea. If damage extends through the mesencephalon and upper pons, respiration becomes shallow, with hyperventilation, but the patient still is relatively hypoxic. If damage extends through the lower pons, respiration involves long inspiratory pauses prior to expiration, called apneustic breathing. Damage extending further into the medulla produces ataxic breathing with irregular patterns, including inspiratory gasps and periods of apnea. This pattern of breathing foreshadows total respiratory failure and death as the basic brain stem centers fail.



"Unfolded" schematic of cerebellum demonstrating regions and lobes



"Unfolded" schematic of cerebellum demonstrating body map areas



Schema of theoretical "unfolding" of cerebellar surface in derivation of above diagram

*F. Netter M.D.*  
JOHN A. CRAIG AD

## CEREBELLUM

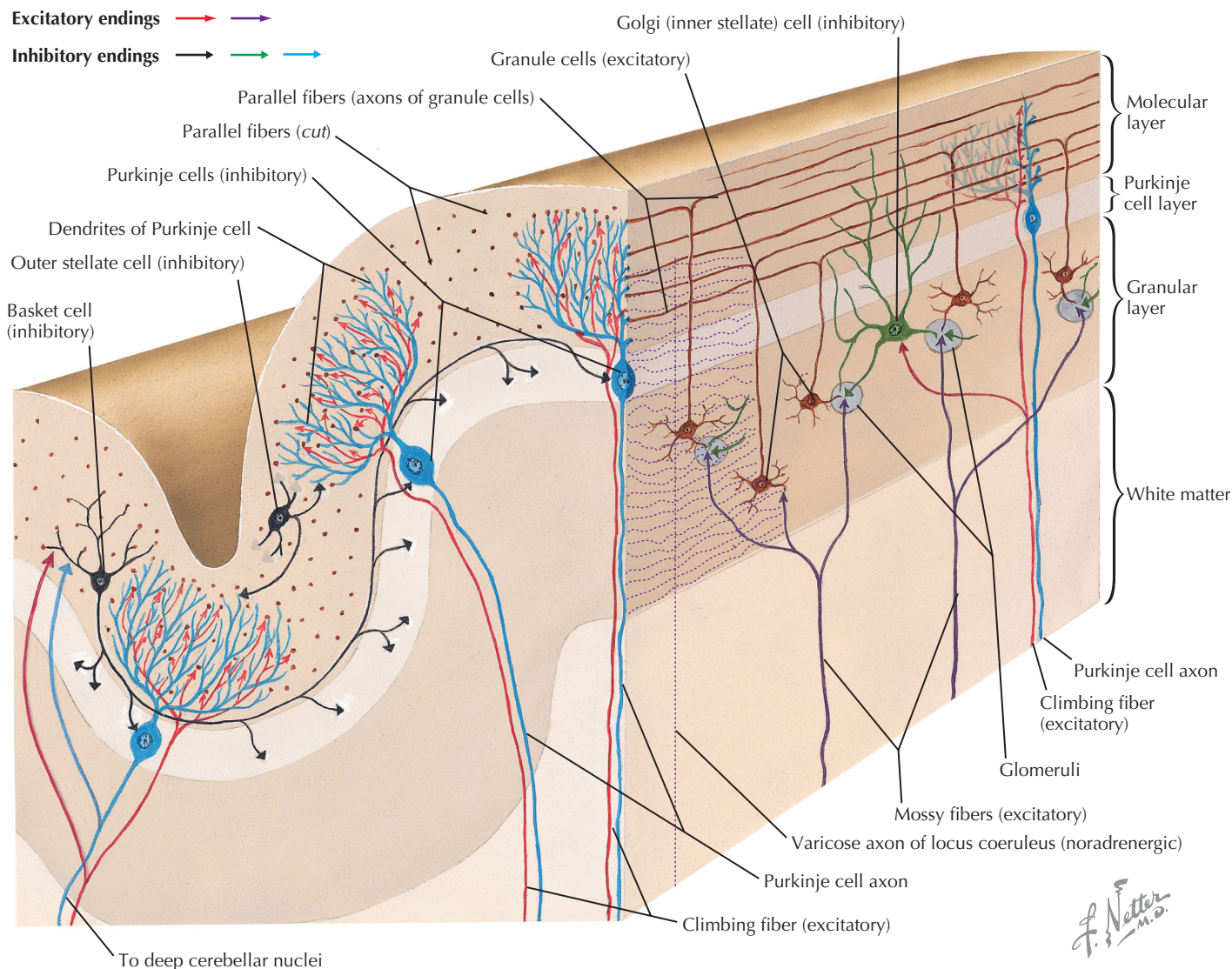
### 15.16 FUNCTIONAL SUBDIVISIONS OF THE CEREBELLUM

The cerebellum is classically subdivided into anterior, middle (posterior), and flocculonodular (FN) lobes, each associated with ipsilateral syndromes, such as stiff-legged gait (anterior lobe); loss of coordination, with dysmetria, action tremor, hypotonus, ataxia, and decomposition of movement (middle lobe); and truncal ataxia (FN lobe). The cerebellum also is

classified according to a longitudinal scheme that is based on cerebellar cortical regions that project to deep cerebellar nuclei, which in turn project to and coordinate the activity of specific UMN cell groups. This scheme includes the vermis and FN lobe (projecting to the fastigial nucleus and the lateral vestibular nucleus); the paravermis (projecting to the globose and emboliform nuclei); and the lateral hemispheres (projecting to the dentate nucleus). Each cerebellar subdivision is interlinked with circuitry related to specific UMN systems.



## Cerebellar Cortex

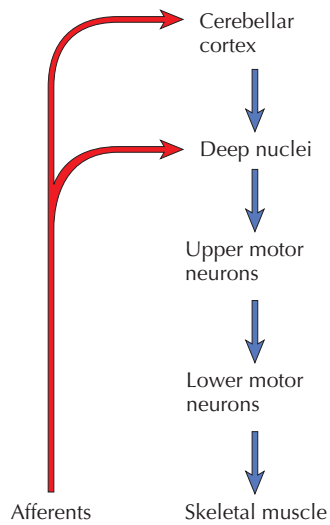
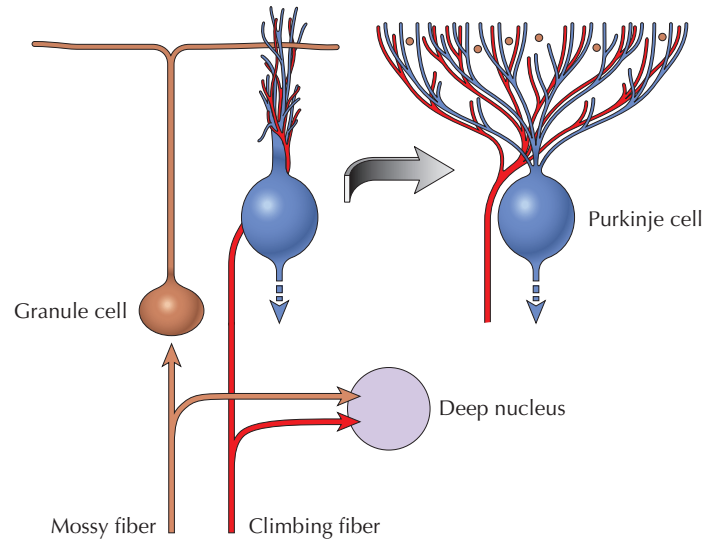
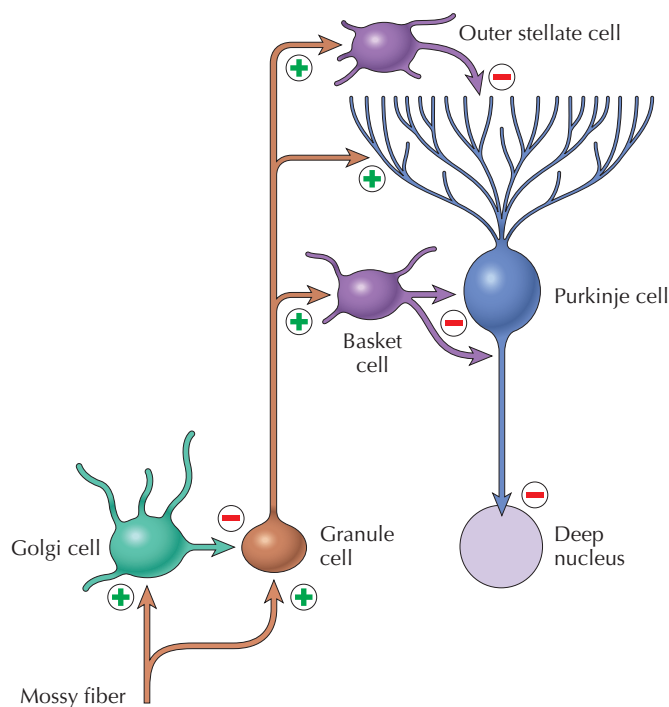
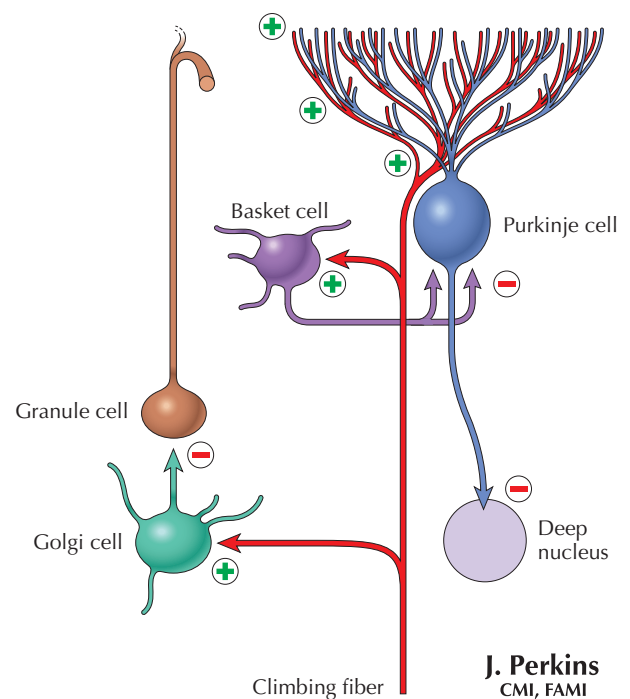


## 15.17 CEREBELLAR NEURONAL CIRCUITRY

The cerebellum is organized into four parts: an outer three-layered cortex, white matter, deep cerebellar nuclei, and cerebellar peduncles that connect with the spinal cord, brain stem, and thalamus. In the cortex, the Purkinje cells (the major output neurons) have their dendritic trees in the molecular layer (arranged in parallel “plates” adjacent to each other), their cell bodies in the Purkinje cell layer, and their axons in the granular layer and deeper white matter. Inputs into the cerebellar cortex arrive as climbing fibers (from inferior olivary nuclei); mossy fibers (all other inputs except monoaminergic); or fine, highly branched, varicose arborizations (noradrenergic and other monoaminergic inputs). The mossy fibers synapse on granule cells, whose axons form an array of parallel fibers that extend through the dendritic trees of several hundred Purkinje cells. Additional interneurons modulate interconnections in the molecular layer (outer stellate cells); at the Purkinje cell body (basket cells); and at granule cell–molecular layer associations (Golgi cells). Noradrenergic axons of locus coeruleus neurons terminate in all three layers and modulate the excitability of other cerebellar connectivities.

## CLINICAL POINT

The cerebellum is a target for significant adverse effects of several types of drugs, sometimes in therapeutic dose ranges and sometimes in toxic dose ranges. Many pharmaceutical agents can exert both direct effects on the cerebellum and more global neurological effects, including ischemia or hypoxia. Cerebellar damage is usually manifested first as impairment of gait, followed later by limb ataxia. These cerebellar side effects often resolve after discontinuation of the medication, but some deficits may remain. Some antiseizure agents, including phenytoin, carbamazepine, and barbiturates, can lead to cerebellar symptoms; after prolonged treatment, particularly with phenytoin, some permanent deficits such as degeneration of Purkinje cells may occur. Valproate may provoke an intention tremor. Some cancer chemotherapeutic agents also can cause adverse cerebellar effects, occasionally permanently. Treatment of psychiatric disorders by multiple pharmaceutical agents, particularly neuroleptics, also can produce adverse cerebellar effects. Toxic damage resulting from exposure to dangerous environmental agents also may damage the cerebellum. Exposure to organophosphate agents and organic solvents may induce cerebellar symptomatology. Exposure to heavy metals, including methylmercury, lead, and thallium, can induce gait disturbance and ataxia.

**A. General Scheme****B. Deep Nuclei Relationship with Afferents****C. Circuitry of Cerebellar Neurons - Mossy Fibers****D. Circuitry of Cerebellar Neurons - Climbing Fibers**

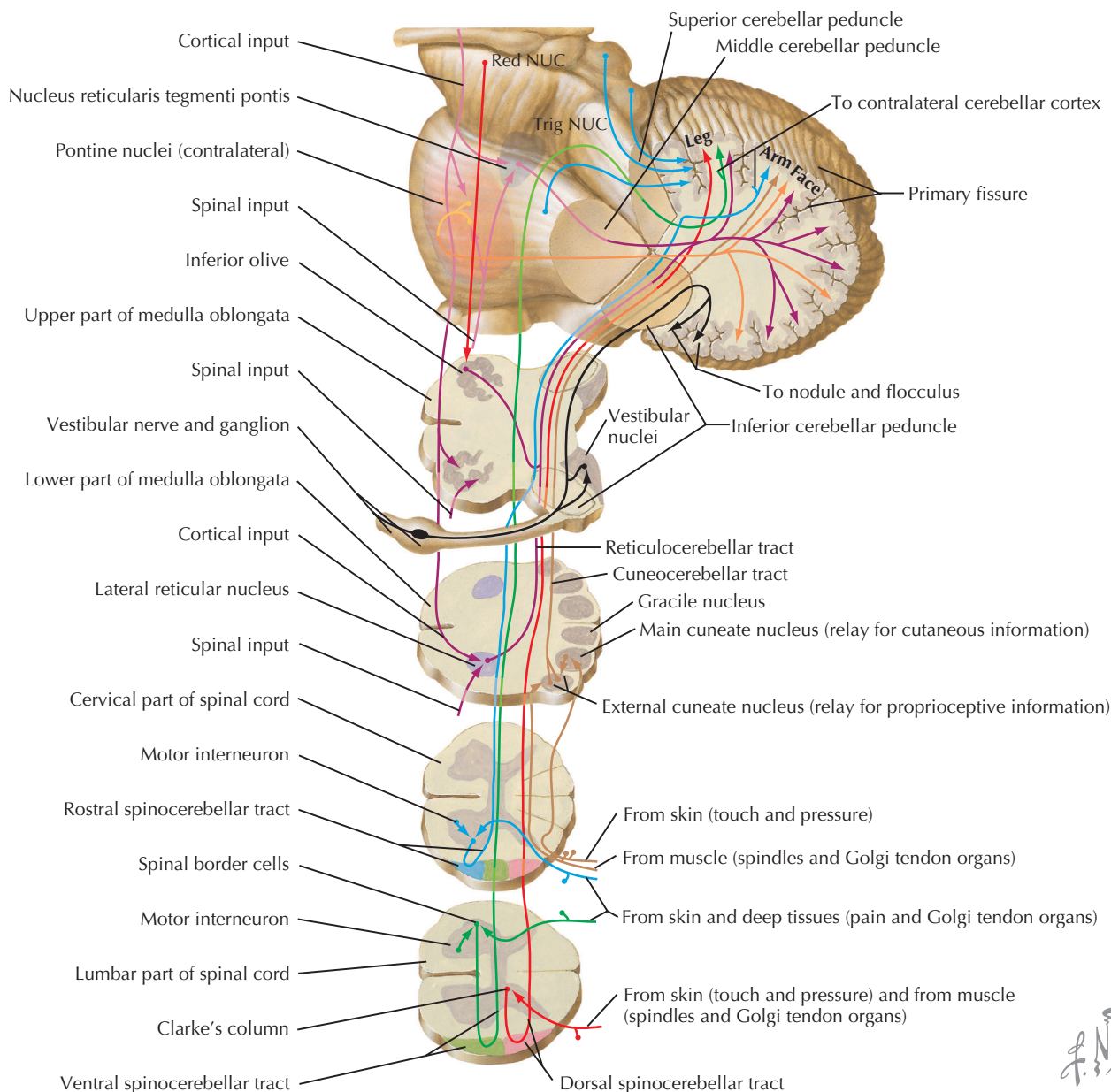
**J. Perkins**  
CMI, FAMI

### 15.18 CIRCUIT DIAGRAMS OF AFFERENT CONNECTIONS IN THE CEREBELLUM

Afferents to the cerebellum include mossy fibers, climbing fibers, and locus coeruleus noradrenergic fibers. The mossy fibers synapse in deep nuclei and on granule cells. The climbing fibers intertwine around a Purkinje cell dendritic tree. The noradrenergic locus coeruleus axons terminate on all cell

types in the cerebellar cortex. The loops and circuits in parts C and D of the figure show interneuronal modulation of afferent connections and Purkinje cell outflow. The entire circuitry of the cerebellar cortex provides fine-tuning of the original processing in the deep cerebellar nuclei. The entire Purkinje cell output to the deep nuclei is mediated by inhibition, using gamma-aminobutyric acid (GABA) as the neurotransmitter.





Note: Afferent connections only to the cerebellar cortex illustrated, not to the deep nuclei

## 15.19 AFFERENT PATHWAYS TO THE CEREBELLUM

Afferents to the cerebellum terminate in both the deep nuclei and the cerebellar cortex in topographically organized zones. The body is represented in the cerebellar cortex in at least three separate regions. Afferents traveling through the inferior cerebellar peduncle include spinocerebellar pathways (dorsal and rostral spinocerebellar tracts, cuneocerebellar tract); the inferior olivary input; RF input from the lateral reticular nucleus and other regions; vestibular input from the vestibular ganglion and vestibular nuclei; and some trigeminal input. The middle cerebellar peduncle conveys mainly pontocerebellar axons carrying crossed corticopontocerebellar inputs. Afferents traveling through the superior cerebellar peduncle include the ventral spinocerebellar tract, visual and auditory tectocerebellar input, some trigeminal input, and noradrenergic locus coeruleus input. The dorsal spinocerebellar tract and cuneocerebellar tract derive mainly from muscle spindle afferent information, whereas the ventral and rostral spinocerebellar tracts derive mainly from Golgi tendon and other receptor organ afferent information.

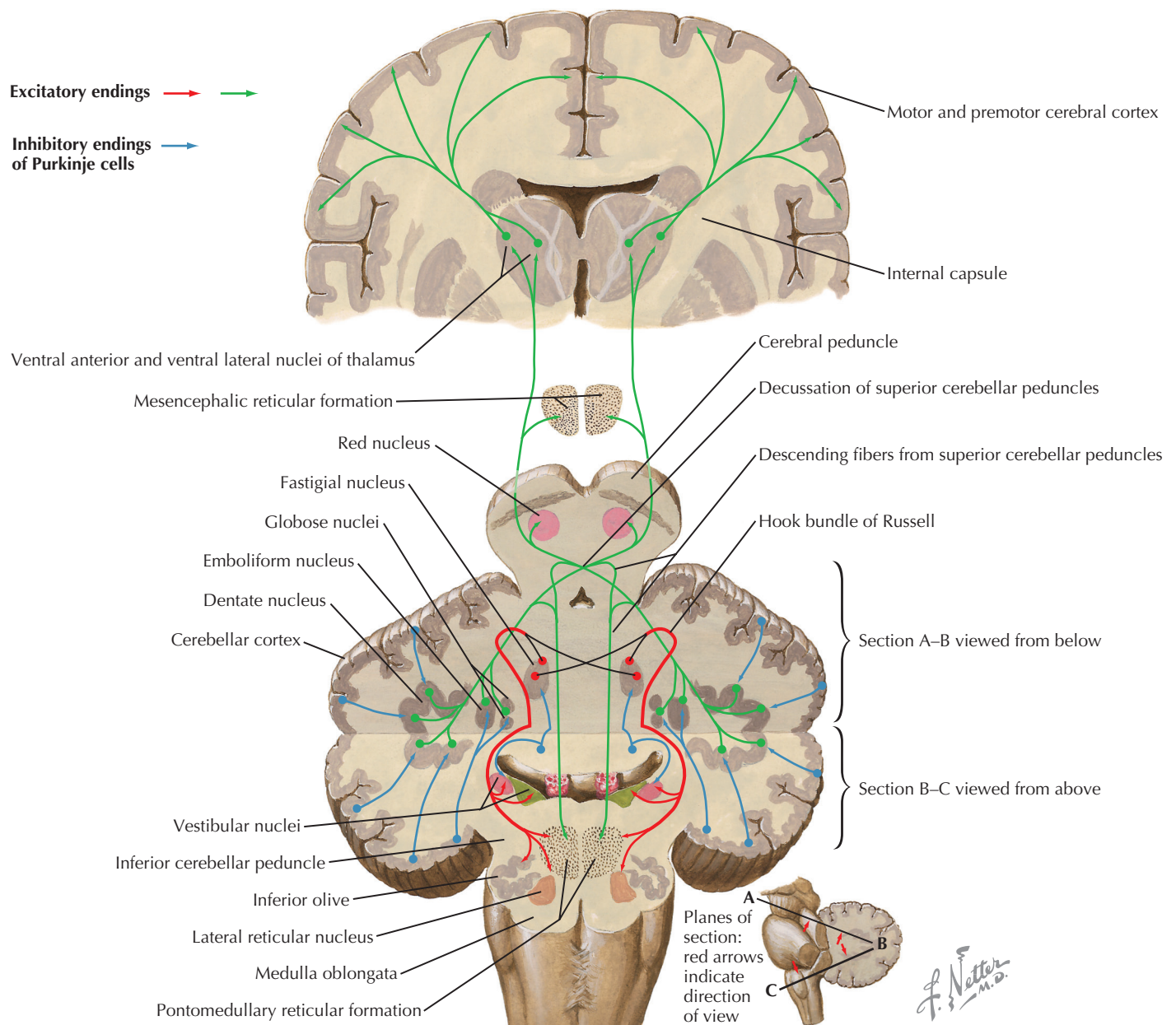
### CLINICAL POINT

Several forms of progressive neuronal degeneration involve cerebellar neurons and connections, including Friedreich's ataxia and olivopontocerebellar atrophy. Friedreich's ataxia is an autosomal recessive disorder that begins in late childhood and progresses over several decades. The disorder commonly starts with ataxia and gait dysfunction, dysmetria and decomposition of movement, and dysarthria. Spastic motor involvement and sensory losses also may occur. Neuropathological examination reveals degeneration of primary afferents and of axons in the spinal cord white matter, especially the dorsal and lateral funiculi, including the spinocerebellar tracts. Some axonal damage also may occur in both the peripheral nervous system and the central nervous system, but the cerebellum itself is usually not a focus of direct neuronal degeneration.

Olivopontocerebellar atrophy is a progressive, mainly autosomal dominant, neurodegenerative disorder that affects adults in midlife. This disorder commonly begins with gait abnormalities and progresses to full-blown cerebellar dysfunction with limb ataxia and dysarthria. Additional symptoms, such as chorea, dystonia, and rigidity, suggest some degenerative involvement of the basal ganglia as well. Neuropathological examination usually reveals neurodegeneration of the cerebellar cortex, the inferior olivary nuclei, and the pontine nuclei. As a consequence, the inferior and middle cerebellar peduncles are diminished. Additional degenerative changes in the cerebral cortex and descending UMN pathways and in the basal ganglia also are commonly present.

*F. Netter M.D.*





### 15.20 CEREBELLAR EFFERENT PATHWAYS

Efferents from the cerebellum derive from the deep nuclei. Projections from the fastigial nucleus exit mainly through the inferior cerebellar peduncle and terminate mainly ipsilaterally in the lateral vestibular nucleus and in other vestibular nuclei as well as in pontine and medullary reticular nuclei that give rise to the reticulospinal tracts; there, they primarily modulate the activity of the vestibulospinal and reticulospinal UMN pathways. Axons from neurons of the globose and emboliform nuclei project mainly contralaterally through the decussation of the superior cerebellar peduncle to the red nucleus, with a smaller contribution to the VL nucleus of the thalamus; primarily, they modulate activity of the RST. Axons from neurons in the dentate nucleus project mainly contralaterally through the decussation of the superior cerebellar peduncle to the VL and to a lesser extent to the VA nuclei of the thalamus; mainly, they modulate the activity of the corticospinal tract. A small projection from the dentate nucleus also distributes to the

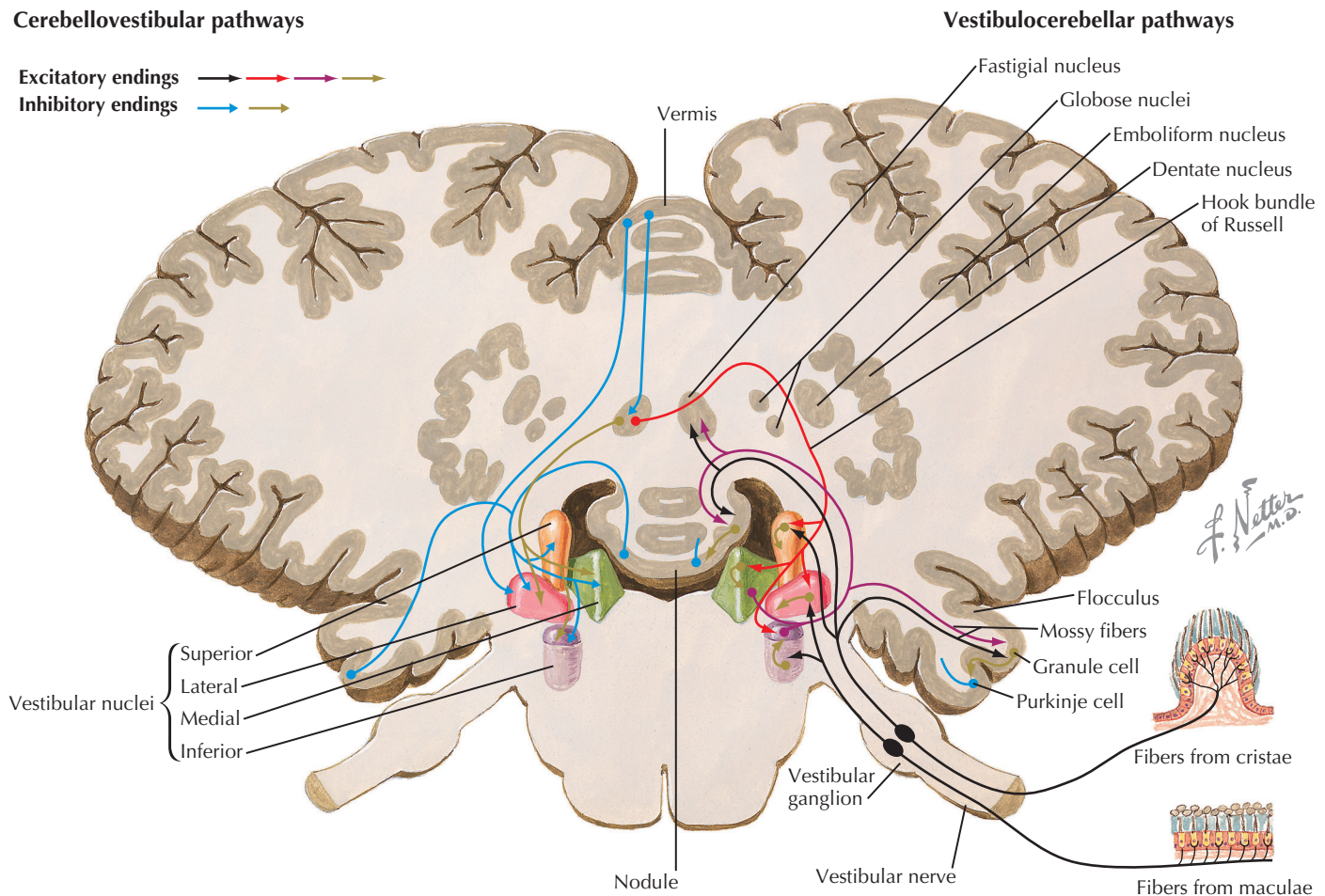
contralateral red nucleus and to brain stem reticular motor nuclei.

#### CLINICAL POINT

Paraneoplastic syndrome is a relatively uncommon, progressive disorder that causes damage to the cerebellum and other neural structures as a secondary effect of cancer. Sometimes the onset of cerebellar symptomatology may precede the detection of the cancer. One major hypothesis about the cause of this disorder is the presence of an immune reaction in which antibodies generated by the immune system against some epitope associated with the cancer cross-react with neural targets. The Purkinje cells appear to be a major target of these immunoglobulin G antibodies. The syndrome often is triggered or exacerbated by chemotherapy or radiation therapy. The entire cerebellum may be targeted, and symptoms may include gait disturbance, ataxia of the limbs with accompanying cerebellar symptoms, dysarthria, and oculomotor coordination problems. Other possible targets of paraneoplastic syndrome include the cerebral cortex and its UMN projections as well as peripheral nerves.

## Cerebellovestibular pathways

Excitatory endings →  
Inhibitory endings →



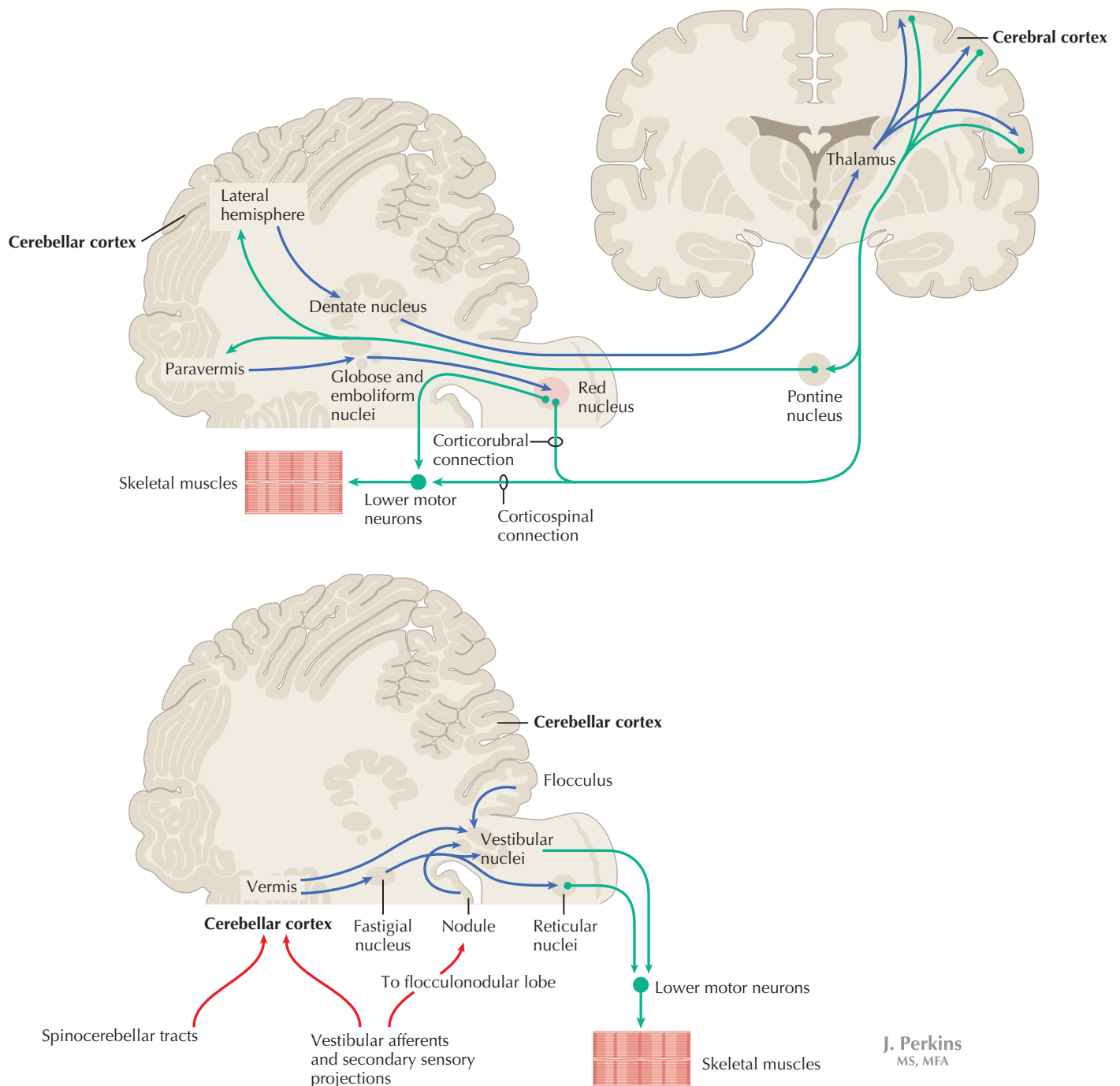
### 15.21 CEREBELLOVESTIBULAR AND VESTIBULOCEREBELLAR PATHWAYS

Primary sensory vestibular inputs terminate in the four vestibular nuclei and in the fastigial nucleus and the cerebellar cortex of the vermis and FN lobe. The vestibular nuclei also project to the cerebellar cortex of the vermis and FN lobe. Purkinje cells in the vermis and FN lobe, in turn, project back to the vestibular nuclei and the fastigial nucleus. The fastigial nucleus projects to the vestibular nuclei and to the pontine and medullary medial reticular formation. Thus, primary and secondary vestibular neurons project to the fastigial nucleus and cerebellar cortex, and both the cerebellar cortex and deep nuclei project back to the vestibular nuclei. This extensive reciprocal vestibulocerebellar circuitry regulates basic spatial position and body tone and posture.

#### CLINICAL POINT

Alcohol consumption may result in acute or chronic dysfunction of the cerebellum and its pathways. Acutely, alcohol intoxication can cause global cerebellar dysfunction, including staggering gait, limb

ataxia, dysmetria, dysdiadochokinesia, dysarthria, and oculomotor dysfunction. Cerebellar testing for alcohol intoxication in the field involves tandem walking, finger-to-nose testing, speech patterns and coordination, and gait testing. These more global effects of alcohol on the cerebellum generally subside with catabolism of the alcohol. Chronic alcoholism results in more permanent damage to the cerebellum, with a particular initial predilection for the anterior lobe of the cerebellum and the vermis (paleocerebellum). The patient may show a staggering, broad-based gait with a stiff-legged movement. The mechanism of this unusual appearance of cerebellar damage (in contrast to the hypotonic, ataxic gait that occurs with global cerebellar damage, particularly in the lateral hemispheres) appears to be removal of the anterior cerebellar influence, via cerebellovestibular connections, on the lateral vestibular nucleus, disinhibiting this extensor-dominant system. This anterior cerebellar syndrome may diminish if the patient stops drinking. With further alcohol exposure, the entire cerebellum may become damaged, leading to the classic appearance of global cerebellar dysfunction, including gait disturbance, hypotonia, limb ataxia, dysarthria, and uncoordinated extraocular involvement. In addition to direct toxicity from alcohol, neural damage may also occur because of vitamin deficiencies, liver dysfunction, and other metabolic aspects of alcoholism. Other parts of the brain, including the cerebral cortex, also can be significantly damaged in chronic alcoholism.

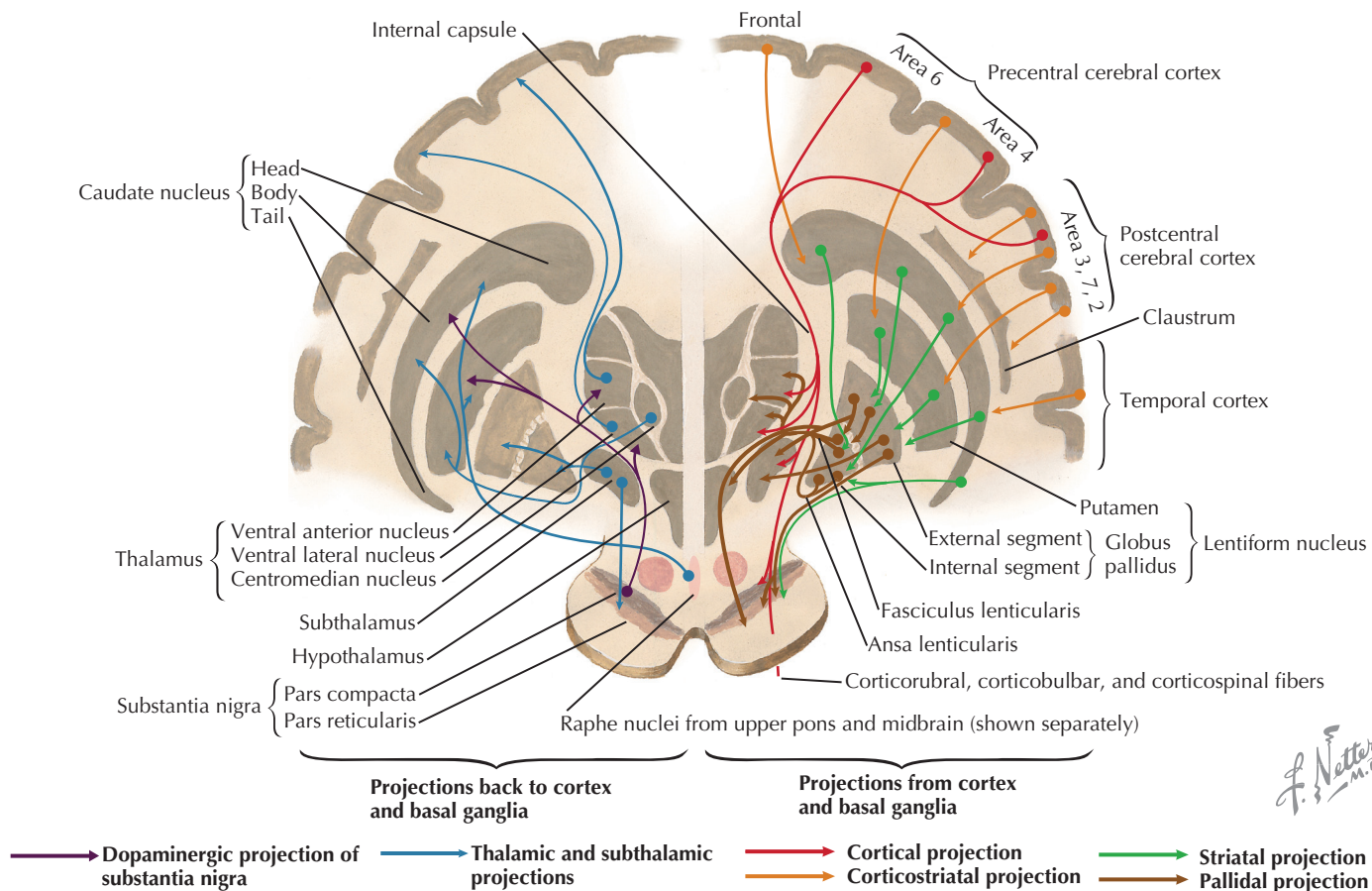


### 15.22 SCHEMATIC DIAGRAMS OF EFFERENT PATHWAYS FROM THE CEREBELLUM TO UPPER MOTOR NEURON SYSTEMS

The lateral cerebellar hemisphere connects through the dentate nucleus with nuclei VA and VL of the thalamus; the major thalamic inputs to the cells of origin of the CST in the motor cortex, and with the supplemental and premotor cortices. The paravermal cerebellar cortex connects through the globose and emboliform nuclei with the red nucleus, cells of origin for the RST. The cerebellar connections to the cells of origin for the CST and RST are mainly crossed, and these UMN systems

cross again before terminating on LMNs. Thus, the cerebellum is associated with the ipsilateral LMNs through two crossings. The vermis and FN lobe connect with the fastigial nucleus and lateral vestibular nuclei. The fastigial nucleus projects mainly ipsilaterally to cells of origin of the vestibulospinal and reticulospinal tracts, exerting mainly an ipsilateral influence on spinal cord LMNs through these UMN systems. The lateral vestibular nucleus is the source of the lateral vestibular tract, which exerts a marked extensor influence on ipsilateral LMNs of the spinal cord.





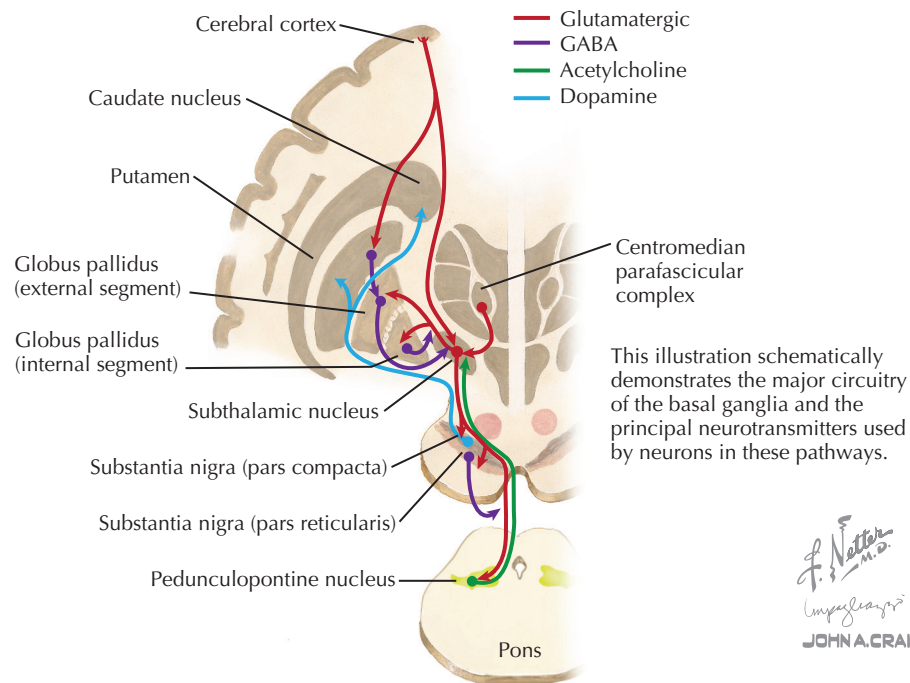
## BASAL GANGLIA

### 15.23 CONNECTIONS OF THE BASAL GANGLIA

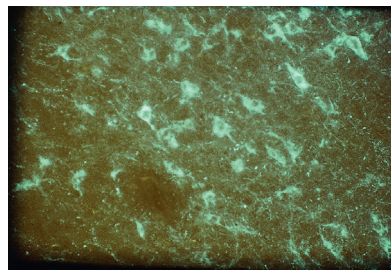
The basal ganglia consist of the striatum (caudate nucleus and putamen) and the globus pallidus. The substantia nigra (SN) and the subthalamic nucleus (STN), which are reciprocally connected with the basal ganglia, are often included as part of the basal ganglia. Inputs into the basal ganglia from the cerebral cortex, the thalamus (intralaminar nuclei), the SN pars compacta (dopaminergic input), the subthalamic nucleus, and rostral raphe nuclei (serotonergic input), are directed mainly toward the striatum. Inputs from the STN are directed mainly toward the globus pallidus. The striatum projects to the globus pallidus. The internal segment of the globus pallidus projects to the thalamus (VA, VL, and centromedian nuclei), and the external segment projects to the STN. The VA and VL thalamic nuclei provide input into the cells of origin of the corticospinal tract. Damage to basal ganglia components often results in movement disorders. Damage to the dopamine neurons in SN pars compacta results in Parkinson's disease (characterized by resting tremor, muscular rigidity, bradykinesia, and postural instability).

### CLINICAL POINT

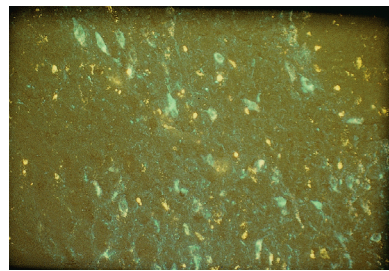
Disorders of the basal ganglia are frequently referred to as movement disorders and were previously called involuntary movement disorders. Despite the conspicuous presence of motor-related symptoms, the basal ganglia also are involved in cognitive and affective processing, particularly in assisting the cerebral cortex to select wanted subroutines of activity and to suppress unwanted patterns. The basal ganglia assist in providing a connection between motivation and emotional context on one hand and movement on the other. Observations of discrete infarcts of parts of the basal ganglia have revealed such abnormalities as abnormal positioning of parts of the body with the presence of increased tone (dystonia) and other movements such as athetosis (slow, writhing movements) or chorea (brisk, dancelike movements). With caudate nucleus damage, more cognitive and affective symptoms may occur, such as apathy and loss of initiative, slowed thinking, and blunted emotional reactivity (abulia), possibly related to the interconnections between the caudate nucleus and the prefrontal cortex. In the classic movement disorders, as in the progressive neurodegenerative diseases, there is a mixture of symptoms showing loss of action, such as bradykinesia (difficulty in initiating movements or diminished movements such as blinking), and symptoms showing an excess of action, such as rigidity, athetosis, chorea, or dystonia. As an example of excess movement, Tourette's syndrome involves tics and involuntary vocalizations, sometimes accompanied by echolalia, grunts and vocal spasms, explosive cursing, and hyperactive behavior, often starting in childhood. Treatment strategies have included use of D2 dopamine antagonists such as haloperidol.



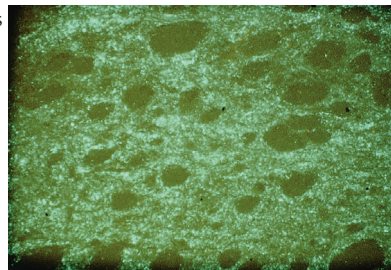
**A.** Substantia nigra pars compacta dopaminergic neurons in young adulthood. GA fluorescence histochemistry.



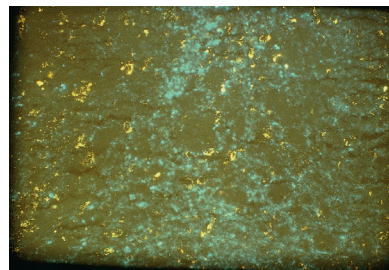
**B.** Substantia nigra pars compacta dopaminergic neurons in old age, demonstrating diminished numbers of neurons and the presence of yellow-staining lipofuscin (aging pigment). GA fluorescence histochemistry.



**C.** Dopaminergic nerve terminals in the caudate nucleus in young adulthood. GA fluorescence histochemistry.



**D.** Dopaminergic nerve terminals in the caudate nucleus in old age, demonstrating diminished density and number of dopaminergic terminals, and the presence of yellow-staining lipofuscin pigment. GA fluorescence histochemistry.

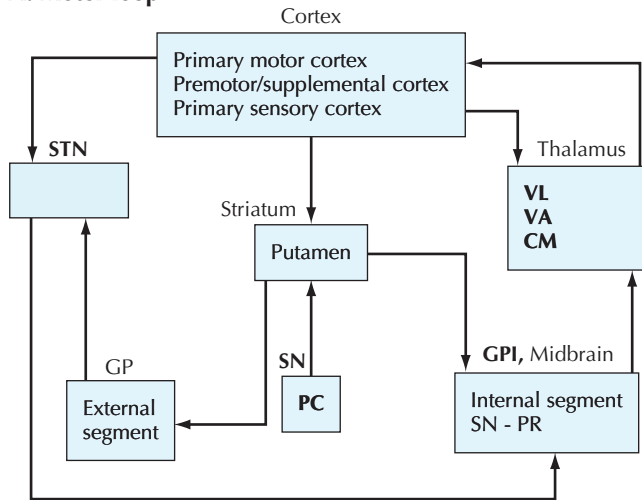
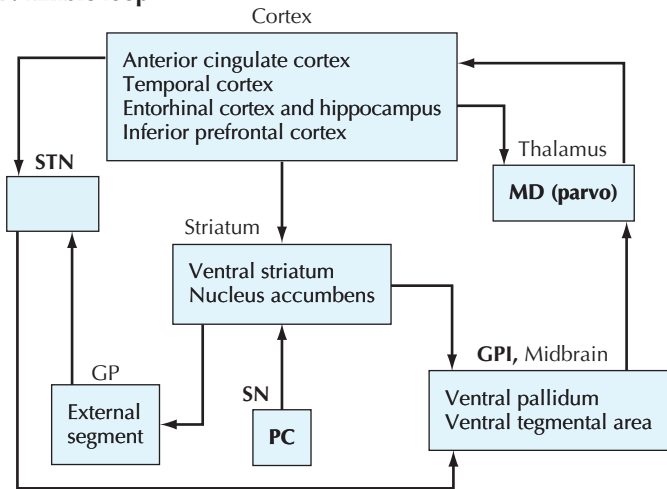
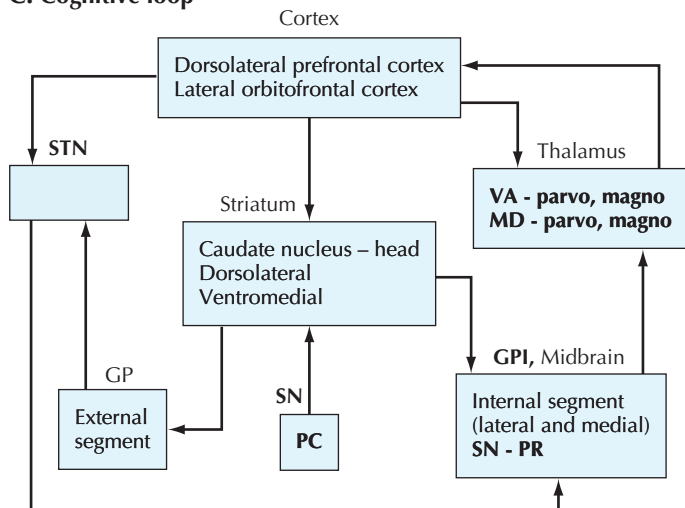
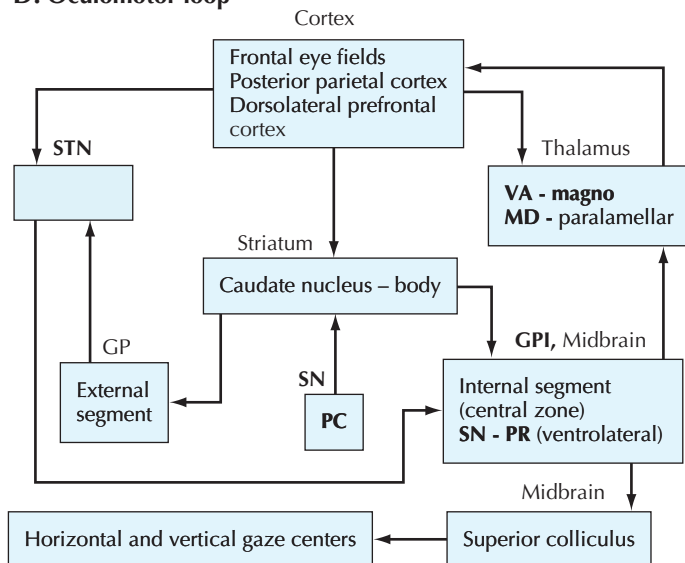


## 15.24 SIMPLIFIED SCHEMATIC OF BASAL GANGLIA CIRCUITRY AND NEUROCHEMISTRY

### CLINICAL POINT

In Parkinson's disease, the pars compacta of the substantia nigra shows loss of pigmented (melanin-containing) neurons that use dopamine as their major neurotransmitter. Both the substantia nigra and the target of the axonal projections, the caudate nucleus and putamen, are severely depleted of their dopamine content. By the time symptoms of Parkinson's disease are clinically evident, at least 50% (and sometimes as much as 80%) of the dopamine neurons in the pars compacta of the substantia nigra have degenerated. Neurons in the substantia nigra sometimes demonstrate Lewy inclusion bodies or neurofibrillary tangles, further evidence of the degenerative process in Parkinson's disease. The neuropathology of Parkinson's disease

sometimes also includes the degeneration of dopamine neurons in the ventral tegmental area of the midbrain, of serotonergic neurons in the raphe nuclei, of cholinergic neurons in nucleus basalis, and of other pigmented neurons in regions such as the dorsal (motor) nucleus of CN X. Although the dopamine deficit in the substantia nigra is the most conspicuous pathological hallmark of Parkinson's disease, these other degenerative processes may contribute to some of the symptoms. The major manifestations of Parkinson disease include both negative and positive (excessive) symptomatology, including (1) resting tremor (approximately 2 cps), which dissipates with movement (i.e., not a movement tremor); (2) muscle rigidity (*lead pipe rigidity*), in which limb musculature shows resistance to passive movement through all ranges of movement, both flexion and extension (NOT similar to spasticity); (3) bradykinesia (difficulty initiating movement or halting movement once it is initiated); and (4) postural instability. Also, sometimes present are head tremor (titubation), rigid facies (fixed, austere-appearing facial expression), and depression.

**A. Motor loop****B. Limbic loop****C. Cognitive loop****D. Oculomotor loop**

CM = Centromedian nucleus  
 GPI = Globus pallidus internal segment  
 magno = Magnocellular  
 MD = Medial dorsal nucleus

parvo = Parvocellular  
 PC = Pars compacta  
 PR = Pars reticulata  
 SN = Substantia nigra

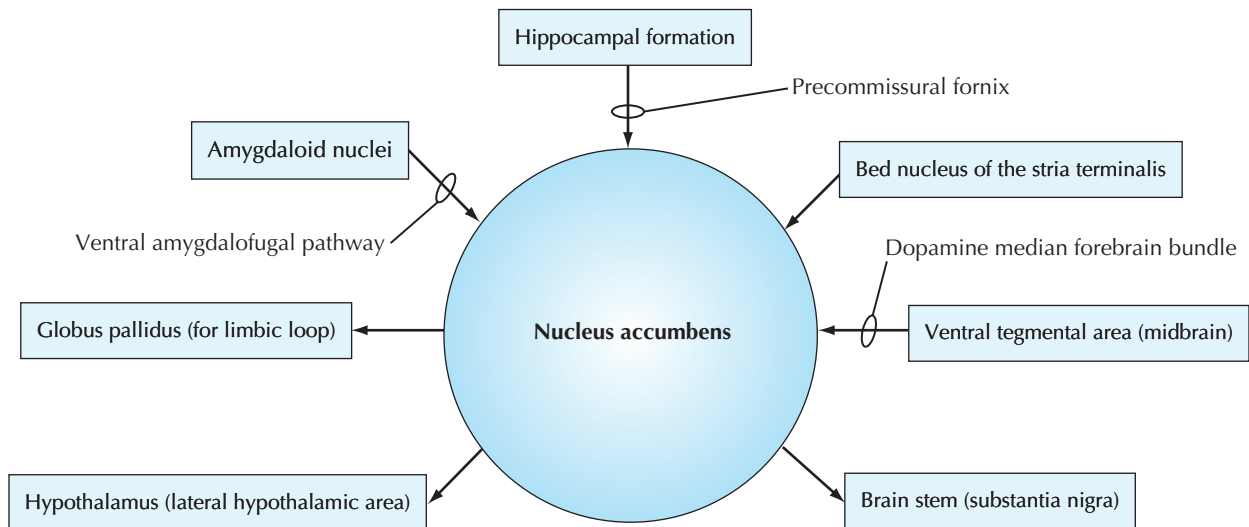
STN = Subthalamic nucleus  
 VA = Ventral anterior nucleus  
 VL = Ventrolateral nucleus

## 15.25 PARALLEL LOOPS OF CIRCUITRY THROUGH THE BASAL GANGLIA

The corticostriatal, striatopallidal, and pallidothalamic connections form parallel loops for motor, limbic, cognitive, and oculomotor circuitry. The motor circuitry is processed through the putamen; the limbic circuitry through the ventral pallidum and nucleus accumbens; the cognitive circuitry through the head of the caudate nucleus; and the oculomotor circuitry through the body of the caudate nucleus. Connections through

the globus pallidus and the pars reticulata of the substantia nigra or ventral tegmental area then project to appropriate regions of the thalamus to link back to the cortical neurons of origin for the initial corticostriatal projections. These parallel loops through the basal ganglia and the cortex serve to modulate specific subroutines of cortical activity distinct to the appropriate function. The pars compacta of the substantia nigra may act as the principal interconnections among these parallel loops.





**Connections of Nucleus Accumbens**

### 15.26 CONNECTIONS OF NUCLEUS ACCUMBENS

Nucleus accumbens is located at the anterior end of the striatum in the interior of the ventral and rostral forebrain (see Figure 13.12). Inputs are derived from limbic structures (amygdala, hippocampal formation, bed nucleus of the stria terminalis) and from the ventral tegmental area of the midbrain via a rich dopaminergic projection. Nucleus accumbens is central to motivational states and addictive behaviors. It also appears to be a principal region in brain reward circuits associated with joy, pleasure, and gratification. The involvement of nucleus accumbens with a specific limbic basal ganglia loop (via globus pallidus) helps to provide motor expression of emotional responses and accompanying gestures and behaviors.

#### CLINICAL POINT

The *extended amygdala* refers to forebrain circuitry involved in processing risk-or-reward perception. This circuitry includes the bed nucleus of the stria terminalis and nucleus accumbens. These forebrain structures have interconnections with the corticomedial and central nuclei of the amygdala (see Plate 16.34 for a summary of amygdaloid circuitry). The bed nucleus of the stria terminalis is involved in processing uncertainty and uncertain threats or risks, in contrast to amygdaloid processing of more specific threats or risks. Nucleus accumbens is involved in processing control of behavioral actions in the face of uncertain threats or risks, and in concert with the amygdala and frontal cortex, is involved with active avoidance behavior (see the work of Joseph LeDoux and colleagues).

When the amygdala and the extended amygdala are activated by potential threats, a quick unconscious response from thalamic input (not the fine-grain analytical lemniscal thalamic components) prepares the brain stem circuitry for needed action. If the amygdaloid-related processing is sent to the prefrontal cortex (medial and lateral) and the parietal cortex, then conscious awareness of the threat and appropriate decision making regarding that threat are activated. More specific threats are processed through the amygdala and specific thalamic projections through sensory cortices to the prefrontal cortex.

**CLINICAL POINT**

See Fig. 14.9. The varicella-zoster virus of childhood chickenpox can reside as a latent virus in dorsal root ganglia, the trigeminal sensory ganglia, and other sensory ganglia. During immunosuppression (medication, cancers, chronic stressors), the reactivation of this virus can cause painful eruptions in the distribution of a sensory nerve root or a division of the trigeminal nerve; this condition is commonly known as shingles or herpes zoster (postherpetic) neuralgia. The most common sites are the thoracic nerve roots or the ophthalmic division ( $V_1$ ) of the trigeminal nerve. The skin erupts with vesicles and a sharp, radiating or burning pain is felt in the region of the eruptions. Sometimes the painful sensations (dysesthesias) occur several days before the eruptions appear. A particular risk related to the ophthalmic division of CN V is corneal ulcerations and subsequent opacities. The nerve, the ganglion, and sometimes the surrounding tissues show inflammatory reactivity. Usually, with combined antiviral therapy and analgesics, the eruptions can subside within a week or so. However, the postherpetic neuralgia, with burning pain, can last for weeks to months and may require the same type of treatment that other neuropathic pain syndromes (reflex sympathetic dystrophy or complex regional pain syndrome) require, including analgesics, tricyclic antidepressants to alter the pain threshold, membrane-stabilizing agents, anti-inflammatory medication, and other approaches.

**CLINICAL POINT**

See Fig. 15.9. The rubrospinal tract, arising from magnocellular neurons of the red nucleus, is part of a cortico-rubro-spinal system that may represent an indirect corticospinal pathway. Rubrospinal tract connections are contralateral and have mainly indirect effects (through interneurons) on both alpha and gamma LMNs. Some authors believe that the rubrospinal tract has a minor role in humans, although observations of decorticate and decerebrate posturing suggest otherwise. In conditions of UMN pathology, the cortico-rubro-spinal system is usually damaged in conjunction with the corticospinal tract (posterior limb of the internal capsule, lateral funiculus of the spinal cord), resulting in a clinical picture of UMN syndrome. Bilateral damage to the forebrain and diencephalon, leaving only the rubrospinal tract, reticulospinal tracts, and vestibulospinal tracts intact, results in a classic UMN appearance bilaterally, with upper limbs in a flexed position and lower limbs in an extended posture (called decorticate posturing). If the lesion extends caudally just below the red nucleus, further removing rubrospinal tract influences, the lateral vestibulospinal tracts are markedly disinhibited, resulting in decerebrate posturing with all four limbs extended. These observations suggest that the rubrospinal system particularly drives flexor activity in the upper extremities and has a lesser role in the lower extremities.

**CLINICAL POINT**

See Fig. 15.11. The reticulospinal tracts originate from isodendritic neurons in the medial portion of the pontine and medullary RF. The pontine RF gives rise to the pontine (medial) reticulospinal tract, which influences mainly proximal musculature. The medullary RF gives rise to the medullary (lateral) reticulospinal tract, which lies more laterally in the spinal cord and influences muscles of the extremities. The reticulospinal tracts help to regulate basic tone and postural responses, sometimes coordinating musculature supplied by LMNs at multiple spinal cord levels. These tracts also may help to direct stereotyped movements such as those involved in extending a limb toward an object. The reticulospinal tracts can selectively influence both alpha- and gamma-LMNs, thus providing a mechanism for activation of static or dynamic gamma-LMNs in conditions of damage to other descending systems, such as the corticospinal and cortico-rubro-spinal systems.

**CLINICAL POINT**

See Fig. 15.14. Vestibular nuclei receive input from the hair cells in the ampullae of the semicircular canals and are connected with extraocular CN motor nuclei, thereby permitting vestibular reflex control of eye movements. This circuitry establishes the connections of the vestibulo-ocular reflex. When the head is rotated in one direction, the lateral semicircular canal initiates a vestibulo-ocular reflex that moves the eyes in the opposite direction, thereby maintaining the position of the eyes. Stimulation of the hair cells on one side of the vestibular apparatus with cold water in the external auditory meatus (the caloric response) provides the brain stem on that side with the neural signaling of apparent movement, and elicits eye movements that would be appropriate to an actual movement, were one occurring. This elicited movement is called caloric nystagmus; it evokes a sense of apparent movement, a tendency to fall to one side, and past-pointing. A lesion or irritative stimulation of the vestibular nerve on one side also gives the neural perception of movement, eliciting pathological nystagmus. If a person rotates in one direction to a greater extent than a simple vestibulo-ocular reflex can easily correct through compensatory eye movements, the eyes will be directed sufficiently far to one side that a quick movement (saccade) will be necessary to refocus them straight ahead. This is called rotational nystagmus, with the slow phase opposite from the direction of movement and the saccade (fast phase) in the direction of the movement; the saccade is neurally directed from the occipital lobe visual cortices. After the rotation stops, the individual will feel as if she or he is still rotating, but in the opposite direction (post-rotational nystagmus), with the saccade in the direction opposite from the original movement, and past-pointing in the direction of apparent movement. If an individual is stationary and stimuli move past the visual field (telephone poles and a person in a moving car), tracking reflexes move the eyes, and a cortically-evoked saccade corrects the eye position with a quick movement of the eyes. This normal physiologic process is called optokinetic nystagmus.

# 16

## AUTONOMIC- HYPOTHALAMIC-LIMBIC SYSTEMS

### Autonomic Nervous System

- 16.1 General Organization of the Autonomic Nervous System

### Hypothalamus and Pituitary

- 16.2 General Anatomy of the Hypothalamus
- 16.3 Sections through the Hypothalamus: Preoptic and Supraoptic Zones
- 16.4 Sections through the Hypothalamus: Tuberal Zone
- 16.5 Sections through the Hypothalamus: Mammillary Zone
- 16.6 Schematic Reconstruction of the Hypothalamus
- 16.7 Forebrain Regions Associated with the Hypothalamus
- 16.8 Afferent and Efferent Pathways Associated with the Hypothalamus
- 16.9 Schematic Diagram of Major Hypothalamic Afferent Pathways
- 16.10 Schematic Diagram of Major Hypothalamic Efferent Pathways
- 16.11 Summary of General Hypothalamic Connections
- 16.12 Paraventricular Nucleus of the Hypothalamus: Regulation of Pituitary Neurohormonal Outflow, Autonomic Preganglionic Outflow, and Limbic Activity
- 16.13 Mechanisms of Cytokine Influences on the Hypothalamus and Other Brain Regions and on Behavior
- 16.14 Circumventricular Organs
- 16.15 The Hypophyseal Portal Vasculature
- 16.16 Regulation of Anterior Pituitary Hormone Secretion
- 16.17 Posterior Pituitary (Neurohypophyseal) Hormones: Oxytocin and Vasopressin

- 16.18 Vasopressin (Antidiuretic Hormone) Regulation of Water Balance and Fluid Osmolality
- 16.19 The Hypothalamus and Thermoregulation
- 16.20 Hypothalamic Regulation of Cardiac Function
- 16.21 Short-Term Regulation of Blood Pressure
- 16.22 Long-Term Regulation of Blood Pressure
- 16.23 Neural Control of Appetite and Hunger
- 16.24 Signaling Systems Involved in Regulation of Good Intake, Body Weight, and Metabolism
- 16.25 Neural and Neuroendocrine Roles in the Fight-or-Flight Response
- 16.26 Neuroimmunomodulation

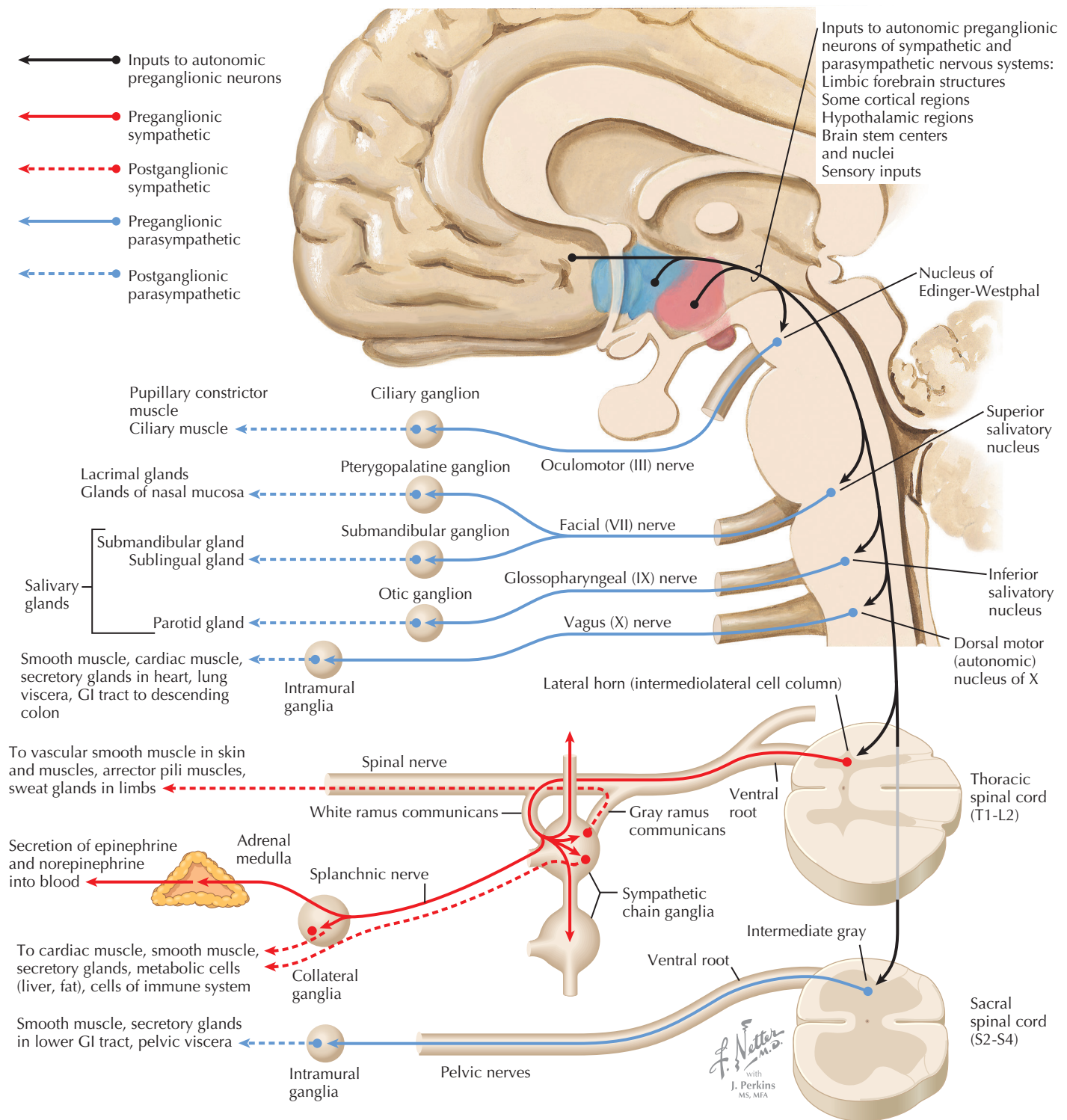
### Limbic System

- 16.27 Anatomy of the Limbic Forebrain
- 16.28 Hippocampal Formation: General Anatomy
- 16.29 Neuronal Connections in the Hippocampal Formation
- 16.30 Major Afferent and Efferent Connections of the Hippocampal Formation
- 16.31 Afferent and Efferent Connections of the Entorhinal Cortex
- 16.32 Major Afferent Connections of the Amygdala
- 16.33 Major Efferent Connections of the Amygdala
- 16.34 Summary of Major Afferents, Efferents, and Interconnections of the Amygdala
- 16.35 Major Afferent and Efferent Connections of the Septal Nuclei
- 16.36 Major Connections of the Cingulate Cortex

### Olfactory System

- 16.37 Olfactory Receptors
- 16.38 Olfactory Pathways





General Organization of the Autonomic Nervous System

## AUTONOMIC NERVOUS SYSTEM

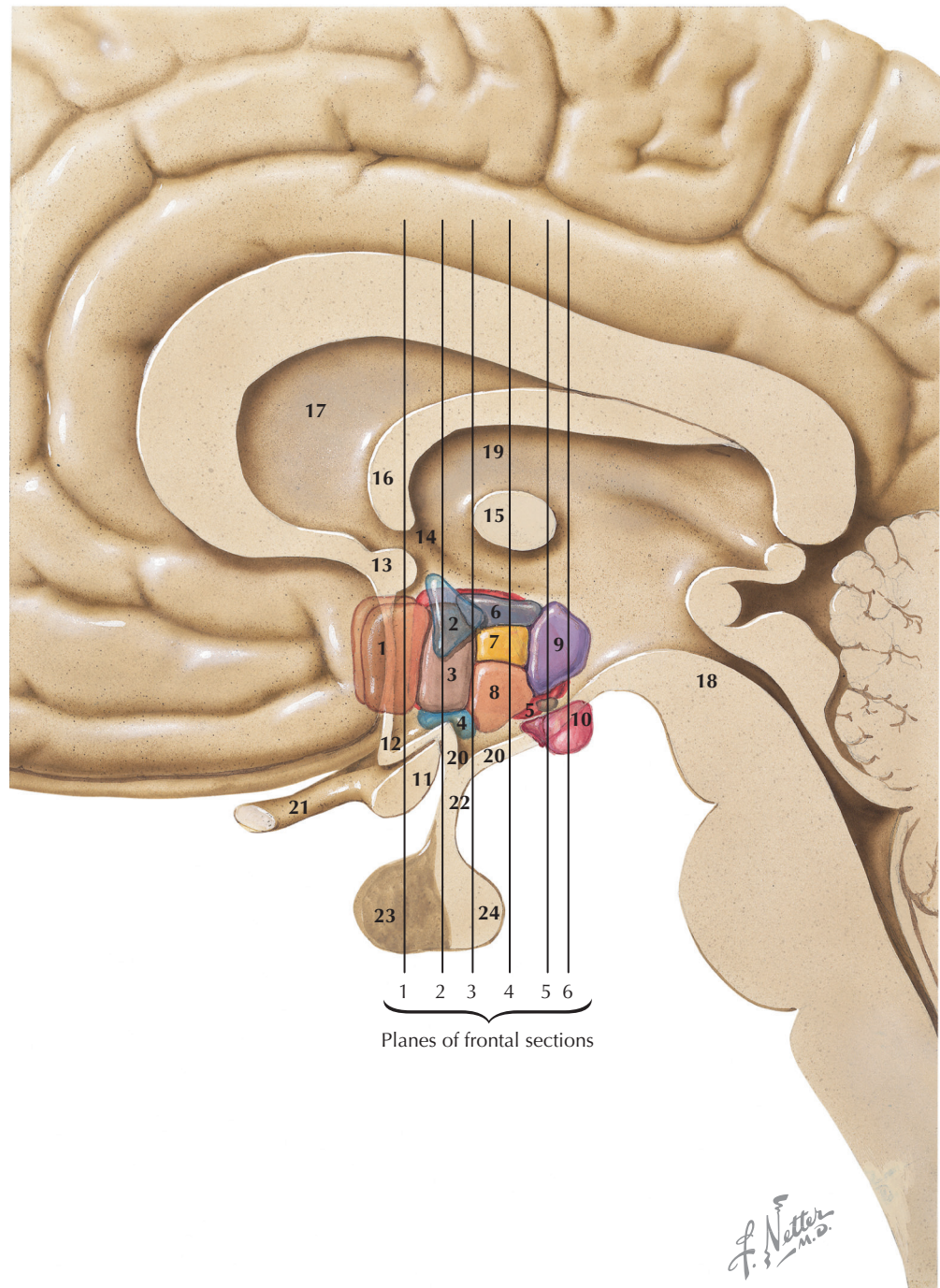
### 16.1 GENERAL ORGANIZATION OF THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system is a two-neuron chain connecting preganglionic neurons through ganglia to visceral target tissues (cardiac muscle, smooth muscle, secretory glands, metabolic cells, cells of the immune system). The sympathetic division (sympathetic nervous system; SNS) is a thoracolumbar (T1–L2) system arising from the intermediolateral cell column of the lateral horn of the spinal cord, acting through chain ganglia and collateral ganglia; it is a system designed for enhancing activities and for fight-or-flight reactions in an emergency. The parasympathetic division (parasympathetic nervous system) is a craniosacral system arising from brain stem nuclei associated with cranial nerves (CNs) III, VII, IX, and X and from the intermediate gray in the S2–S4 spinal cord. Connections from CNs III, VII, and IX act through cranial nerve ganglia; connections from the vagal system and sacral system act through intramural ganglia in or near the target tissue. The parasympathetic nervous system is a homeostatic reparative system. Central connections from the limbic forebrain, hypothalamus, and brain stem regulating the sympathetic and parasympathetic nervous systems' outflow to the body act mainly through connections to vagal and sympathetic preganglionic neurons.

#### CLINICAL POINT

Preganglionic parasympathetic neurons in the brain stem and sacral spinal cord, as well as preganglionic sympathetic neurons in the thoracolumbar spinal cord, send projections to ganglion cells and use acetylcholine as the principal neurotransmitter. The ganglion cells possess mainly nicotinic cholinergic receptors for transducing fast neurotransmission responses. Postganglionic sympathetic neurons use mainly norepinephrine as their neurotransmitter, whereas postganglionic parasympathetic neurons use acetylcholine. Target tissue possesses alpha and beta adrenoceptor subclasses and cholinergic muscarinic receptor subclasses (M1–M3). In the heart, beta1 receptors increase the force and rate of contraction, increase cardiac output, and dilate coronary arteries, whereas M2 receptors decrease the force and rate of contraction and cardiac output. In vascular smooth muscle and smooth muscles of the pupil, ureters, and bladder, alpha1 receptors cause contraction. In blood vessels, alpha2 receptors also cause constriction. In smooth muscle of the tracheobronchial system, uterus, and gastrointestinal tract vasculature, beta2 receptors cause relaxation. Alpha1 receptors cause relaxation of gastrointestinal smooth muscles, and M1 receptors cause slow contraction. M3 receptors cause contraction of most parasympathetic smooth muscle target structures. In salivary glands, alpha1 receptors cause secretion and beta2 receptors cause mucus secretion. In adipose tissue, alpha1 receptors cause glycogenolysis, beta1 receptors cause lipolysis, and alpha2 receptors inhibit lipolysis. In sweat glands, alpha1 receptors cause secretion. In the kidney, alpha1 receptors enhance reabsorption of Na<sup>+</sup>, and beta1 receptors provoke renin release. In liver and skeletal muscles, beta2 receptors cause glycogenolysis. In the pancreas, beta2 receptors stimulate insulin release, and alpha2 receptors inhibit insulin release. On immunocytes, beta-adrenergic receptors decrease natural killer (NK) cell activity and decrease the secretion of Th1 cytokines (interferon-gamma, interleukin 2) by Th1 lymphocytes. The balance of adrenergic and cholinergic neurotransmission determines the relative degree of activation of target tissues, and differential affinity of ligands for the various receptor subclasses helps to determine the final integrative physiological response.

- 1 Preoptic nuclei
- 2 Paraventricular nucleus
- 3 Anterior hypothalamic area
- 4 Supraoptic nucleus
- 5 Lateral hypothalamic area
- 6 Dorsal hypothalamic area
- 7 Dorsomedial nucleus
- 8 Ventromedial nucleus
- 9 Posterior hypothalamic area
- 10 Mammillary body (nuclei)
- 11 Optic chiasm
- 12 Lamina terminalis
- 13 Anterior commissure
- 14 Hypothalamic sulcus
- 15 Interthalamic adhesion
- 16 Fornix
- 17 Septum pellucidum
- 18 Midbrain
- 19 Thalamus
- 20 Tuber cinereum
- 21 Optic nerve
- 22 Infundibulum
- 23 Anterior lobe of pituitary
- 24 Posterior lobe of pituitary



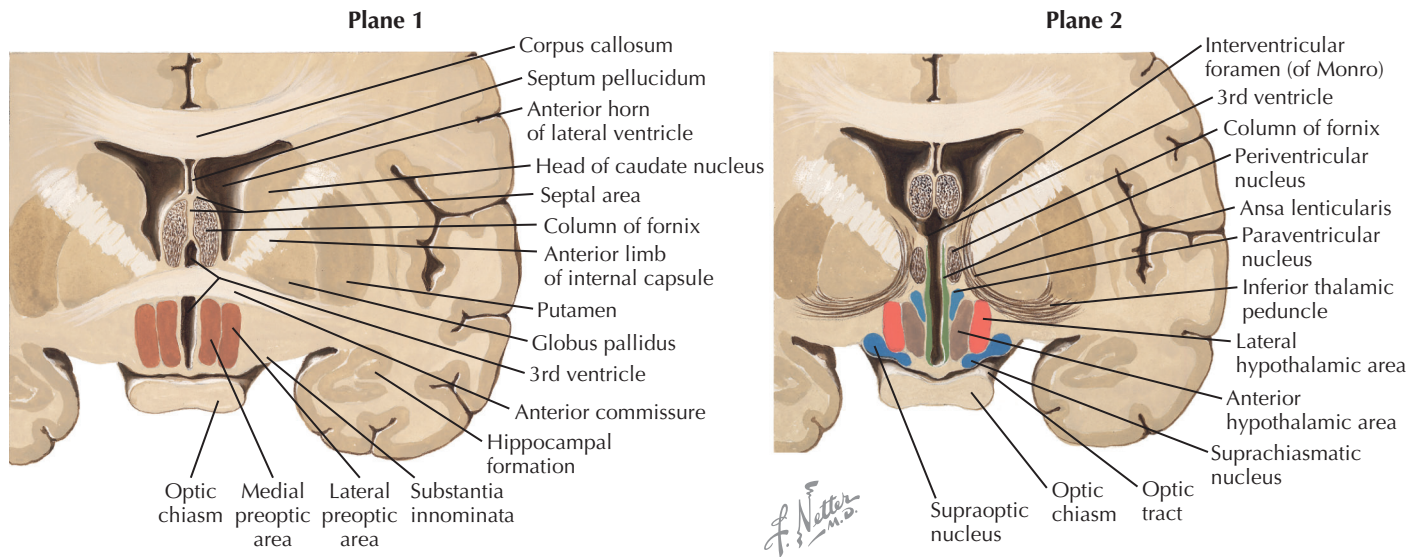
## HYPOTHALAMUS AND PITUITARY

### 16.2 GENERAL ANATOMY OF THE HYPOTHALAMUS

The hypothalamus is a collection of nuclei and fiber tracts in the ventral diencephalon that regulates visceral autonomic functions and neuroendocrine functions, particularly from the anterior and posterior pituitary. Many nuclei are found between the posterior boundary (mammillary bodies) and the anterior boundary (lamina terminalis, anterior commissure) of the hypothalamus; these nuclei are subdivided into four

general hypothalamic zones: (1) preoptic; (2) anterior or supraoptic; (3) tuberal; and (4) mammillary or posterior. From the medial boundary at the III ventricle to the lateral boundary, the nuclei are subdivided into three general zones or areas: (1) periventricular; (2) medial; and (3) lateral. The pituitary gland is attached at the base of the hypothalamus by the infundibulum (pituitary stalk), which possesses an important zone of neuroendocrine transduction, the median eminence.





### 16.3 SECTIONS THROUGH THE HYPOTHALAMUS: PREOPTIC AND SUPRAOPTIC ZONES

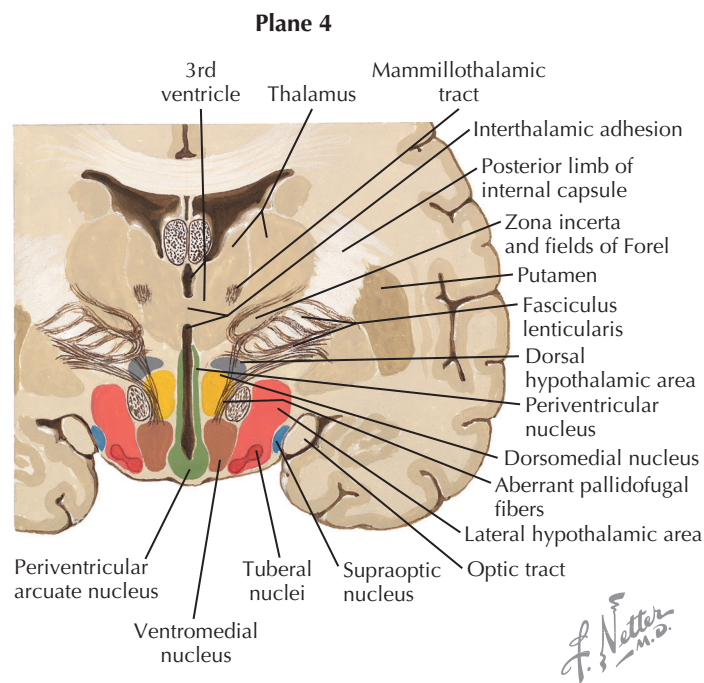
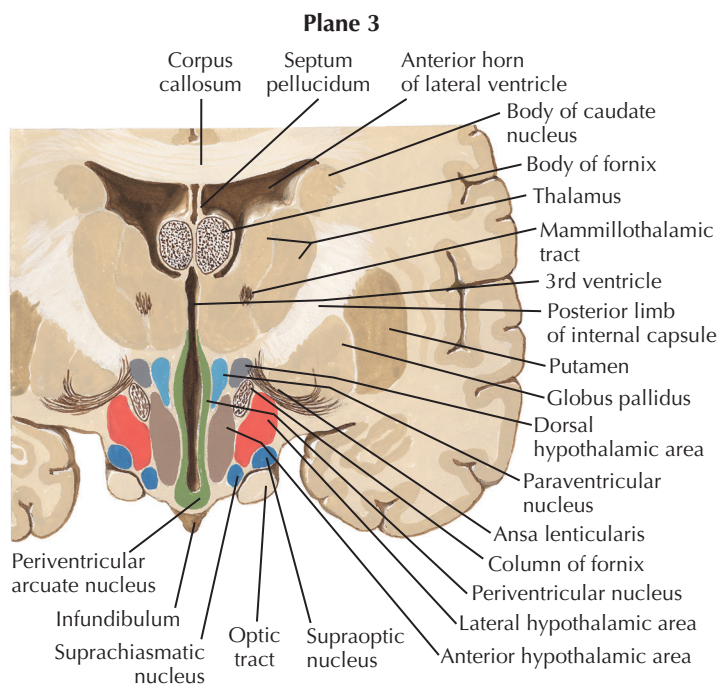
The major nuclei in the preoptic zone (Plane 1) include the medial and lateral preoptic areas. The organum vasculosum of the lamina terminalis (OVLT), a circumventricular organ (with no blood-brain barrier) is present in this hypothalamic area. The major nuclei in the supraoptic (anterior) zone (Plane 2) include the supraoptic (SON) and paraventricular (PVN) nuclei, the suprachiasmatic nucleus, the anterior hypothalamic area, and the lateral hypothalamic area (LHA). Some nuclei such as the PVN have many subregions (such as the magnocellular and parvocellular regions) that contain many collections of chemically specific neurons (20 or more) that have discrete projections and functions. These groups are sometimes intermingled within one subregion of the nucleus.

#### CLINICAL POINT

The hypothalamus and brain stem structures are involved in regulating the sleep-wake cycle. Ablative lesions of the preoptic area result in insomnia. Some preoptic neurons appear to be maximally activated during sleep and may inhibit neurons in the posterior hypothalamus (such as tuberomammillary neurons) that contribute to wakefulness. The LHA also contains neurons involved in wakefulness through the secretion of an activating neuropeptide, hypocretin. Neurons of the LHA activate the tuberomammillary neurons as well as the locus coeruleus in the pons, a noradrenergic cell group with widespread projections to all regions of the central nervous system (CNS) and a major role in arousal and wakefulness. Early epidemics of encephalitis lethargica (sleeping sickness) demonstrated damage to the midbrain and posterior regions of the hypothalamus. This scheme is consistent with a role for the posterior hypothalamus in sympathetic activation and arousal and with a role for the anterior and preoptic hypothalamus in parasympathetic activation and quiet, reparative, homeostatic

functions. Narcolepsy is a condition of episodic periods of overwhelming daytime drowsiness and then an abrupt episode of sleep, even in the middle of an activity. The person then awakens and feels alert. Night-time sleep may be disturbed, but this is not the cause of daytime sleep episodes; patients with narcolepsy go into rapid eye movement sleep in a matter of minutes rather than hours. Many stimuli (e.g., intense emotion, excitement, laughter) may precipitate an episode of cataplexy in which the knees give out, the person falls, and an abrupt sleep episode follows. Sleep apnea is a major sleep disorder, often associated with obesity, in which patients have prolonged periods of apnea, followed by gasping and including disturbed sleep and loud snoring. It is a major risk factor for heart disease.

The suprachiasmatic nucleus (SCN) sits just above the optic chiasm and contains the major neurons of the CNS that act as a “pacemaker” system for the control of diurnal, or circadian, rhythms. The intrinsic pacemaker has a cycle that is a bit longer than 24 hours (studied in humans who lived in caves with no external light cues); however, input from the retina to the suprachiasmatic nucleus entrains the diurnal rhythms to a 24-hour period. These diurnal rhythms drive many hormone and metabolic levels (e.g., cortisol is low in the late evening, high in the morning before rising; melatonin is highest in late evening) and physiological functions (blood pressure and core body temperature are lowest in early morning, highest in late afternoon). Superimposed on these diurnal rhythms are broader factors, such as effects of the sleep-wake cycle, life stress, levels of activity, and other environmental factors. Sleep has a particularly important influence on cortisol rhythms. Disrupted or poor sleep habits can ablate the diurnal cortisol rhythm, leading to a propensity for fat to be deposited in a central abdominal location because of the effects of high cortisol levels. This can contribute to the likelihood of metabolic syndrome, with its elevated inflammatory mediators (C-reactive protein and interleukin [IL]-6) and increased risk for cardiovascular disease, stroke, type II diabetes, and many cancers. The SCN is influenced by a host of limbic and other forebrain influences superimposed on diurnal rhythms. The SCN, in turn, has axonal projections to other regions of the hypothalamus, the locus coeruleus, and limbic sites through which the diurnal regulatory control of these hormones and physiological functions is achieved.



## 16.4 SECTIONS THROUGH THE HYPOTHALAMUS: TUBERAL ZONE

The major nuclei in the tuberal zone (Planes 3 and 4) include the dorsomedial nucleus, the ventromedial nucleus, the periventricular area or nucleus, the arcuate nucleus, the periarculate area (beta-endorphin cells), the tuberal nuclei, the dorsal hypothalamic area, and the LHA. Some nuclei from the supraoptic zone (PVN, SON, LHA) extend caudally into this zone. The median eminence extends from this region, and axons from releasing-factor and inhibitory-factor neurons that control the release of anterior pituitary hormone funnel down to the contact zone, where they release these factors (hormones) into the hypophyseal portal system, which bathes the cells of the anterior pituitary.

### CLINICAL POINT

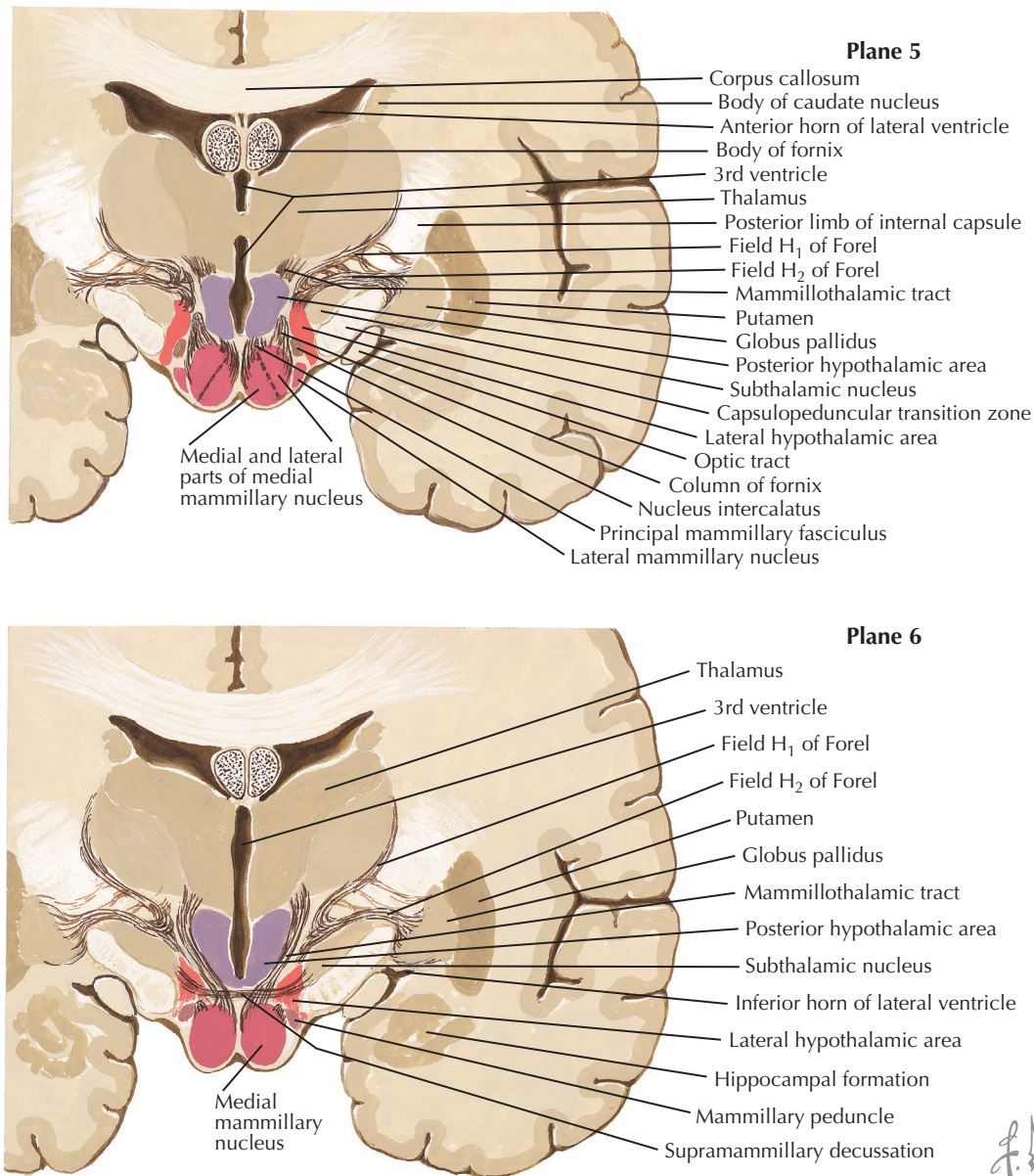
The secretion of hormones by the anterior pituitary gland is regulated by releasing factors (hormones) and inhibitory factors (hormones) that are produced by neurons of the hypothalamus and adjacent sites and are secreted by their axons into the hypophyseal portal vasculature for delivery in extraordinarily high concentrations to cells of the anterior pituitary. A well-known releasing factor is corticotropin-releasing hormone or factor (CRH or CRF), produced by parvocellular neurons of the paraventricular nucleus, which regulates subsequent secretion of adrenocorticotrophic hormone (ACTH) and cortisol. Another important releasing hormone, growth hormone-releasing hormone, is produced by neurons in the arcuate nucleus and delivered by their axons to the hypophyseal portal system. Somatostatin is a growth hormone-inhibitory hormone and is produced by other neurons in the arcuate nucleus as well as elsewhere. These hormones are regulated by neural connections, hormonal influences, and metabolic factors.

Growth hormone (GH) is released in pulsatile bursts during stage 3 and stage 4 sleep, accounting for 70% of GH release. GH release also is stimulated by exercise, acute stressors, hypoglycemia, and intake of

protein, and is suppressed by intake of glucose and many fatty acids. Children who experience emotional deprivation secrete low levels of GH and may fail to grow. Recent studies have shown that mirthful laughter associated with viewing humorous videos markedly stimulates GH secretion and diminishes cortisol and epinephrine secretion. Even more remarkable, when subjects anticipate viewing something humorous, the anticipation itself provokes GH secretion that is as great as or greater than the GH secretion seen in stage 3 and stage 4 sleep.

Sex steroid hormones influence brain development. In a male fetus, the developing testes provide androgens (converted in the brain to estradiol) that influence CNS development in a male pattern during critical developmental periods. All developing fetuses are exposed to maternal estrogen as well as some placental hormones, but the estrogen is bound by alpha-fetoprotein, which protects the female fetus from masculinization by the CNS. One important consequence of fetal exposure to sex steroids is the subsequent hypothalamic control of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland. In females, these hormones are released in a cyclic fashion. In males, FSH and LH are released in steady amounts, a phenomenon dependent upon CNS exposure to estradiol via androgens during fetal development. In the CNS, FSH and LH secretion is controlled by gonadotropin-releasing hormone (GnRH), formerly called luteinizing hormone-releasing hormone. GnRH neurons in the preoptic area project to the contact zone of the median eminence, ending on the hypophyseal-portal vessels. The GnRH neurons are responsive to estrogen in the female brain but not in the male brain, perhaps accounting for the cyclic secretion of FSH and LH in females. The ventromedial (VM) nucleus of the hypothalamus appears to control some aspects of sexual behavior; VM neurons respond to progesterone via receptors in the female brain but not the male brain. The male brain responds behaviorally to circulating androgens but not to estrogen. Anatomically, preoptic and VM neurons show male-female differences in morphological and synaptic features. A specialized portion of the preoptic area, the sexually dimorphic nucleus, is considerably larger in the male brain than in the female brain, apparently triggered by developmental hormonal exposure.





### 16.5 SECTIONS THROUGH THE HYPOTHALAMUS: MAMMILLARY ZONE

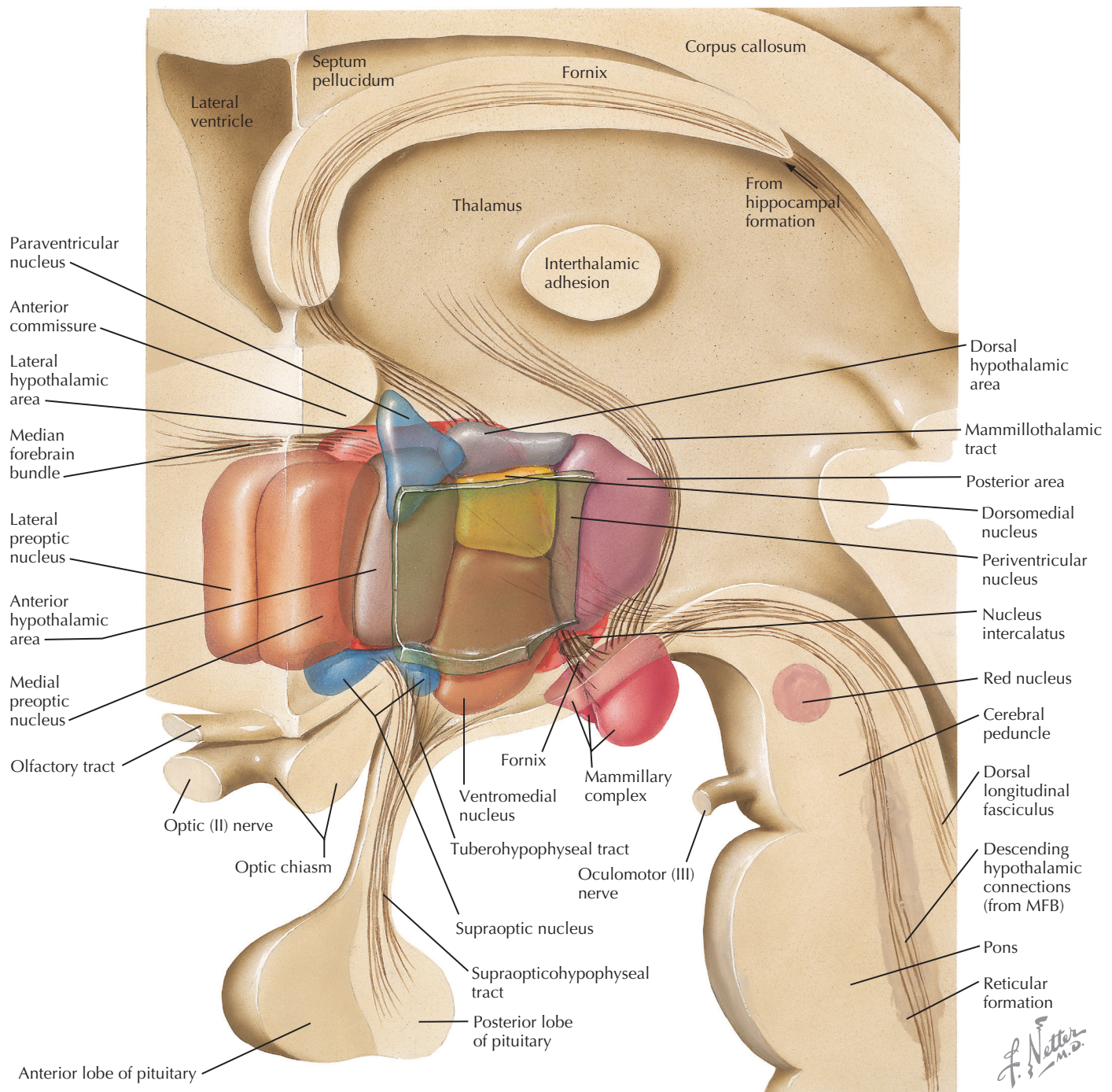
The major nuclei in the mammillary zone (Planes 5 and 6) include the medial and lateral mammillary nuclei, the posterior hypothalamic area, and the LHA. The LHA extends throughout most of the length of the hypothalamus and shows neuronal characteristics seen in the brain stem reticular formation.

#### CLINICAL POINT

In the 1930s, James Papez proposed a brain circuit that was viewed as a substrate for control of emotional behavior and later as a substrate for memory, especially for consolidation of immediate and short-term memory into long-term memory. This circuit includes hippocampal formation (especially the subiculum) via the fornix to the mammillary nuclei (especially medial nuclei); via the mammillothalamic tract to the anterior thalamic nuclei; via the internal capsule to the anterior cingulate cortex; via polysynaptic connections in the cingulum to the

entorhinal cortex, subiculum, and hippocampus. This circuit is proposed as a site of major damage in Wernicke-Korsakoff syndrome, a disorder that is commonly seen in chronic alcoholic patients with a vitamin B<sub>1</sub> (thiamine) deficiency. This syndrome includes Wernicke's encephalopathy and the memory dysfunction of Korsakoff's syndrome. Wernicke's encephalopathy involves a confused and psychotic state involving confabulation (made-up stories derived from a host of confused past memories or experiences), cerebellar ataxia, extraocular and gaze palsies, and nystagmus. Korsakoff amnesic syndrome involves the inability to consolidate immediate and short-term memory into long-term traces (anterograde amnesia) as well as long-term memory loss concerning events that have occurred since the onset of the disease. Degeneration has been described in the mammillary bodies, fornix, hippocampal formation, and anterior and medial dorsal thalamus. However, the extent to which the mammillary nuclei themselves play a role in consolidation of memory traces remains to be shown. Thiamine administration may help to reverse some of the symptoms, but the amnesias may persist. Administration of glucose (carbohydrate loading) without thiamine may cause death as the result of nutritional cardiomyopathy.



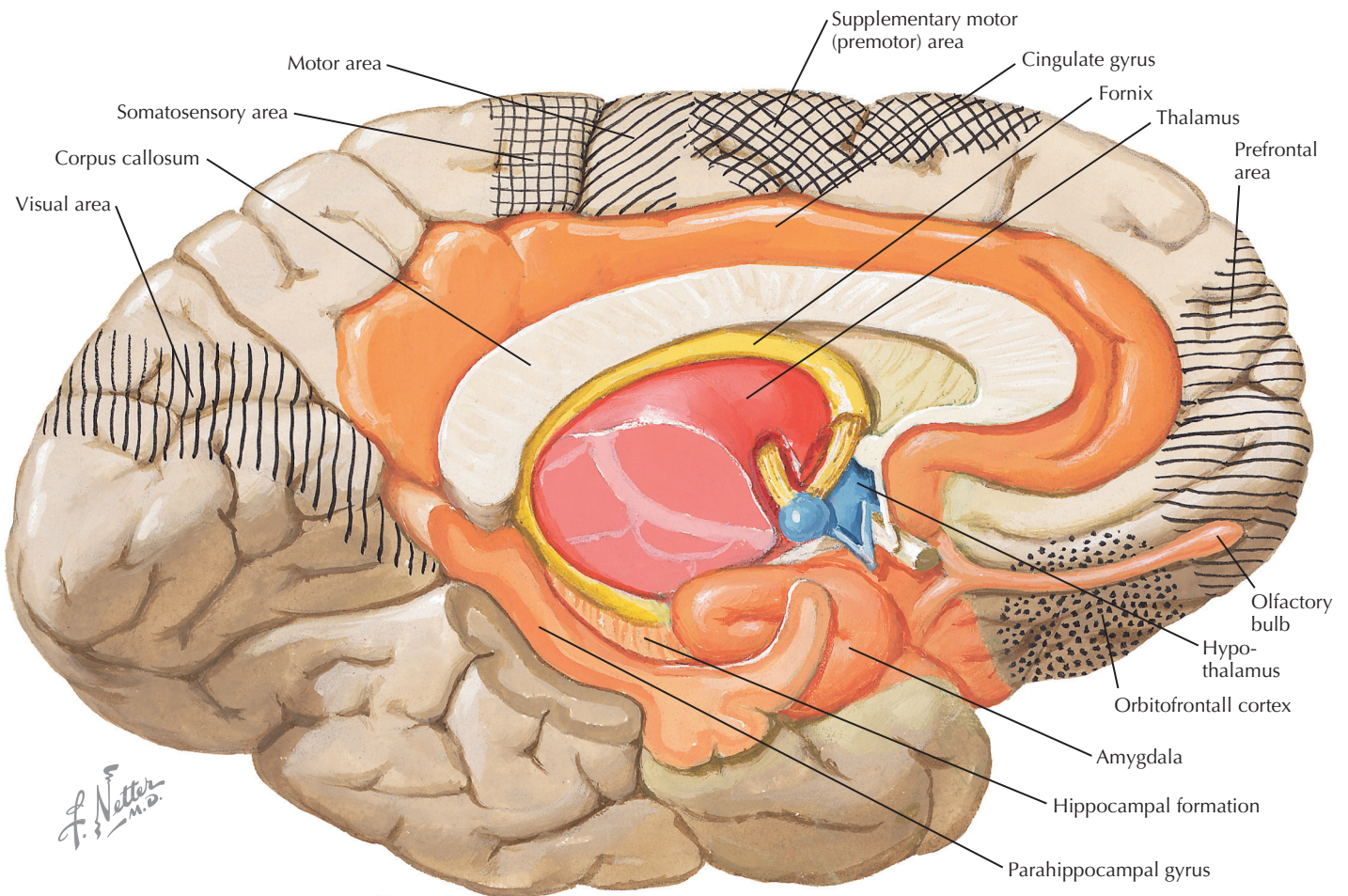


## 16.6 SCHEMATIC RECONSTRUCTION OF THE HYPOTHALAMUS

A schematic three-dimensional reconstruction of the hypothalamus in sagittal section shows the nuclei, areas, and zones that occupy this small, compact region of the diencephalon. Many pathways are represented in this schematic reconstruction, including the fornix, the mammillothalamic tract, the

median forebrain bundle (MFB), the supraopticohypophyseal tract, the tuberohypophyseal (tuberoinfundibular) tract, and brain stem connections with the hypothalamus via the dorsal longitudinal fasciculus, the descending median forebrain bundle, the mammillotegmental tract, and descending connections from the PVN to preganglionic autonomic nuclei.





## 16.7 FOREBRAIN REGIONS ASSOCIATED WITH THE HYPOTHALAMUS

Numerous forebrain regions are intimately connected with the hypothalamus, some through direct fiber projections and others through indirect connections. The important regions of the cerebral cortex include the prefrontal cortex, orbitofrontal cortex, cingulate cortex, insular cortex, parahippocampal cortex, and periamygdaloid cortex. The important subcortical regions of the limbic forebrain include the hippocampal formation, amygdaloid nuclei, and septal nuclei. Important thalamic connections include the medial dorsal and anterior nuclei. Important olfactory connections include the olfactory tract, nuclei, and cortex.

### CLINICAL POINT

The **placebo effect** is a positive change in a patient's symptoms or subjective experience, or in a patient's physiological state, including pain modulation, altered cardiovascular function, and immune reactivity (both innate and acquired), based on the patient's expectations, interactions with health care personnel and treatments, or administration of medication (e.g., a pill) that normally has little direct pharmacological effects. Negative effects from such expectations or interactions are called a **nocebo effect**. The placebo effect has been described as "not real," "not a medicine," "based on belief," and having "no effect on disease processes or illnesses." However, in pharmaceutical testing of highly reactive medications, it is often observed that the placebo is almost as effective as the pharmacological medication for altering clinical outcomes. Placebo effects, often involving condi-

tioned responses, do indeed alter physiological processes, sometimes profoundly, with effects on disease outcome, as happens with conditioned immune responses in which a "placebo" alters lethal outcomes in experimental models of immune-related diseases (see the work of Robert Ader and Nicholas Cohen).

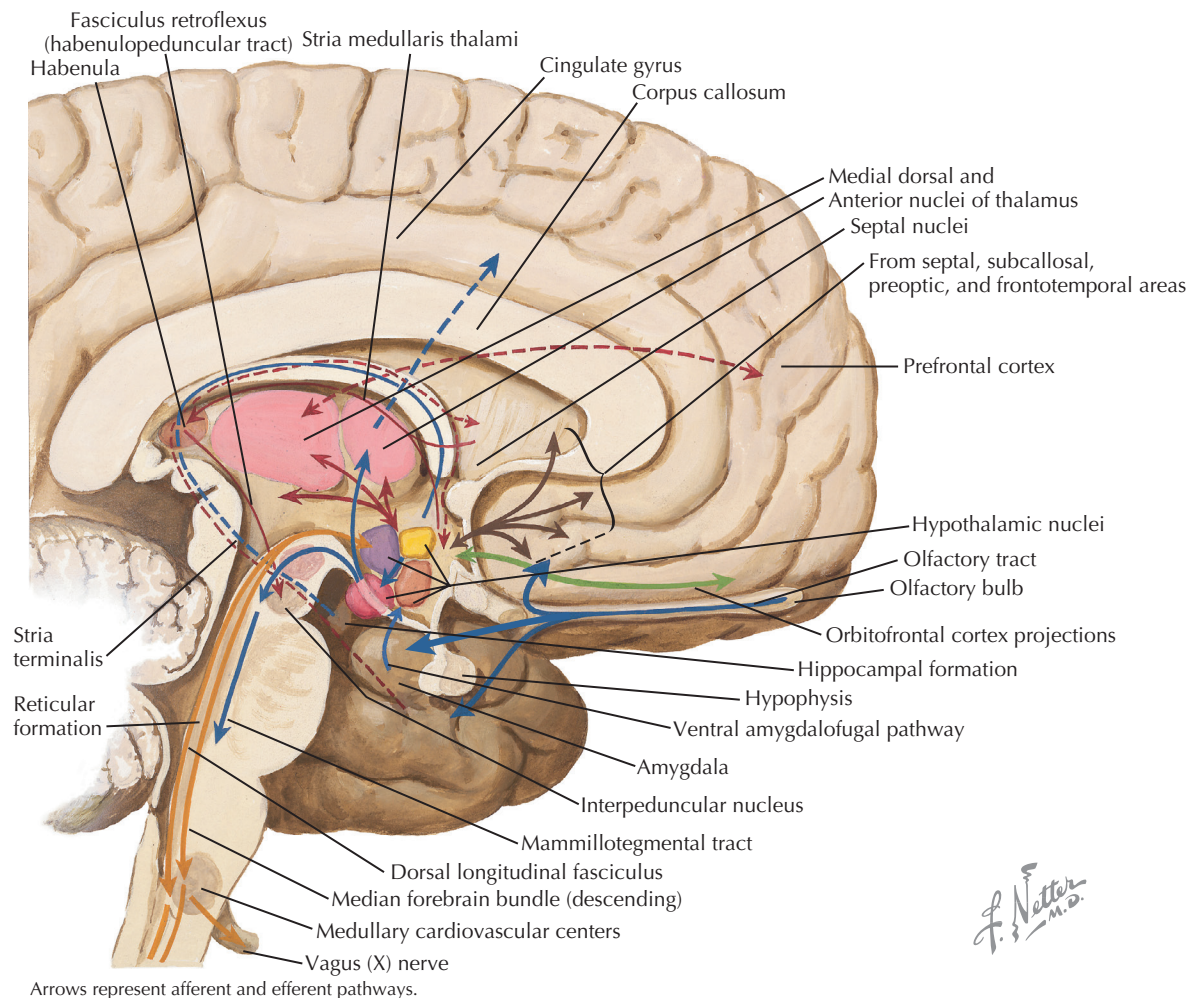
Placebo effects occur through known pathways and circuitry of the brain, including prefrontal cortex, anterior insular cortex, rostral anterior cingulate cortex, some amygdaloid nuclei, and in the brain stem, the periaqueductal gray. These structures act through influences on autonomic and neuroendocrine outflow, as well as by initiating appropriate behavioral responses. Disruption of these forebrain circuits can prevent the physiological effects of the placebo. Neurotransmitter systems such as endorphins, cannabinoids, dopamine and other catecholamines, and cortisol are involved in mediating placebo effects, and their pharmacological alterations (e.g., naloxone blockade of opioid receptors in placebo administration for pain) can prevent the physiological and behavioral alterations seen in the placebo effect.

Use of placebo effects and acknowledgment of conditioned responses have an important role in clinical medicine and disease treatment. It is likely that many complementary medicine approaches utilize, in part, placebo effects with their appropriate forebrain circuitry and neurotransmitter systems. This is consistent with the "relaxation response" described and documented by Herb Benson and colleagues, and the use of guided imagery, meditation, qi gong, and other parasympathetic-inducing practices.

See references for thoughtful discussions of placebo effect:

Kaptchuk TJ, Miller FG: Placebo effects in medicine. *N Engl J Med* 373:8–9, 2015.

Finnias DG, Kaptchuk TJ, Miller FG, Bennett F: Biological, clinical, and ethical advances of placebo effect. *Lancet* 375:686–695, 2010.



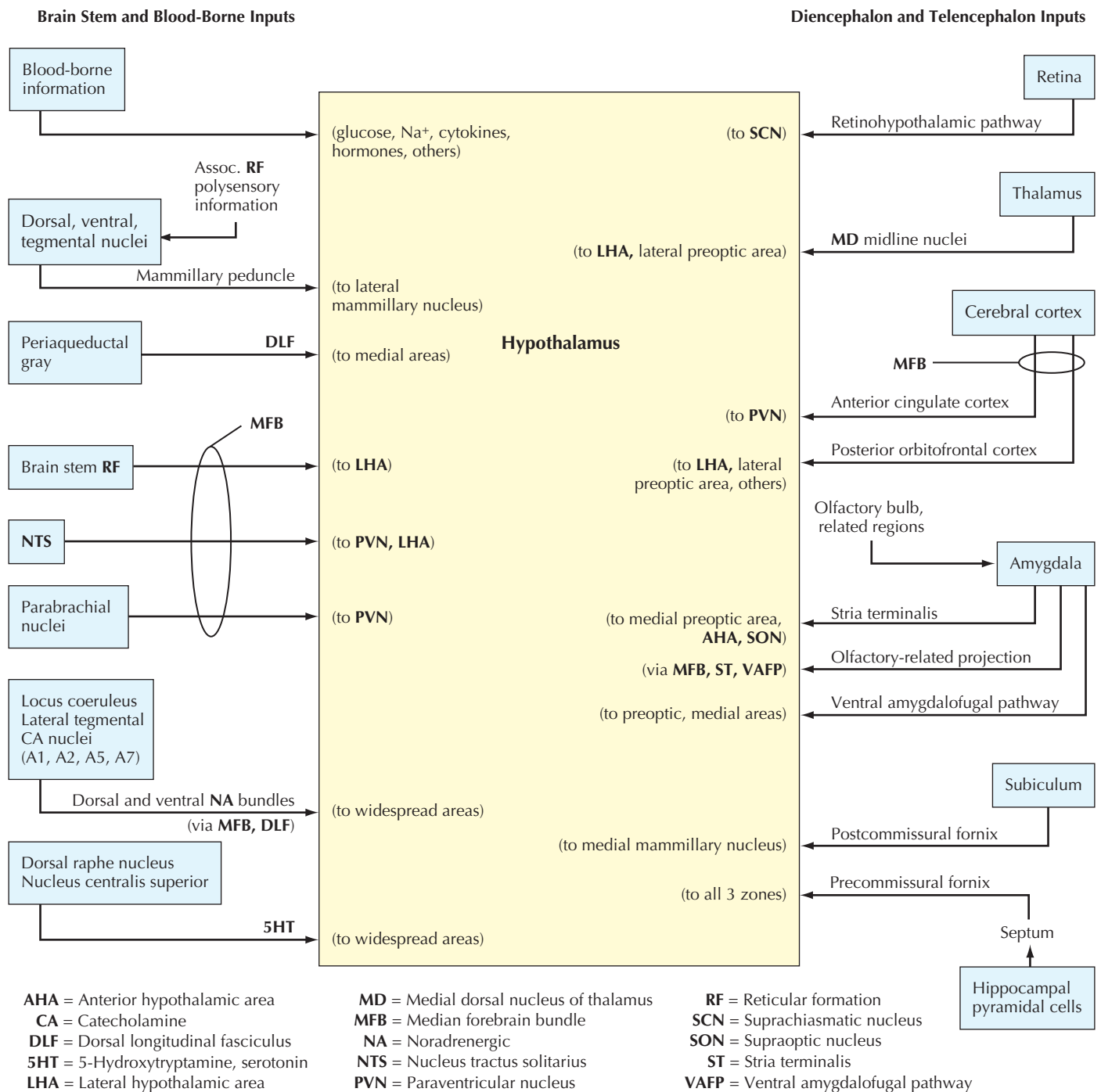
## 16.8 AFFERENT AND EFFERENT PATHWAYS ASSOCIATED WITH THE HYPOTHALAMUS

Hypothalamic connections are numerous and complex. Some regions of the cerebral cortex (prefrontal, orbitofrontal) and thalamus (anterior) send axonal projections directly to the hypothalamus. Diverse afferent pathways arise from the hippocampal formation and the subiculum (fornix), amygdaloid nuclei (stria terminalis, ventral amygdalofugal pathway), and habenula (fasciculus retroflexus). The retina sends direct retinohypothalamic fibers to the suprachiasmatic nucleus of the hypothalamus. Numerous brain stem projections, some compact and some diffuse, ascend to the hypothalamus by multiple pathways (not shown here). Efferent connections from the hypothalamus include those to the median eminence (from multiple nuclei), the posterior pituitary (supraoptico-hypophyseal tract), the septal nuclei and the anterior perforated substance (median forebrain bundle), the thalamus (mammillothalamic tract), and many brain stem and spinal cord sites (dorsal longitudinal fasciculus, median forebrain bundle, mammillotegmental tract, direct connections from PVN to preganglionic neurons, and others). The habenula receives afferents from the septal nuclei, lateral preoptic hypothalamic region, and anterior thalamic nucleus via the stria medullaris thalami, and sends projections to the preoptic area and septal nuclei.

### CLINICAL POINT

The hypothalamus receives inputs from the hippocampal formation and subiculum, amygdaloid nuclei, habenula, retina, some cortical areas, and many brain stem regions; a good number of these inputs are limbic forebrain and brain stem connections. The role of the hypothalamus is to regulate the visceral milieu and neuroendocrine secretion, particularly via the anterior and posterior pituitary. The efferents of the hypothalamus reflect this role and are directed to the posterior pituitary and contact zone of the median eminence (for control of anterior pituitary hormonal secretion), some limbic forebrain structures, and widespread areas of the brain stem and spinal cord that are involved in autonomic and visceral regulation. These connections help to coordinate appropriate behavioral responses to external and internal inputs and perceived challenges in the environment. The posterior and lateral hypothalamic regions are particularly involved in sympathetic drive and activational responses, such as the acquisition of food and water, the increase of core body temperature, sympathetic arousal, activities involved in aggressive interactions with the environment, and wakefulness states. Many of these activities are coordinated through connections in the median forebrain bundle. In contrast, the anterior and medial hypothalamic regions are particularly involved in parasympathetic functions, such as satiation, decreased core body temperature, quiet and reparative homeostasis-related activities, and sleep. Many of these activities are coordinated through connections in the dorsal longitudinal fasciculus and other descending pathways.

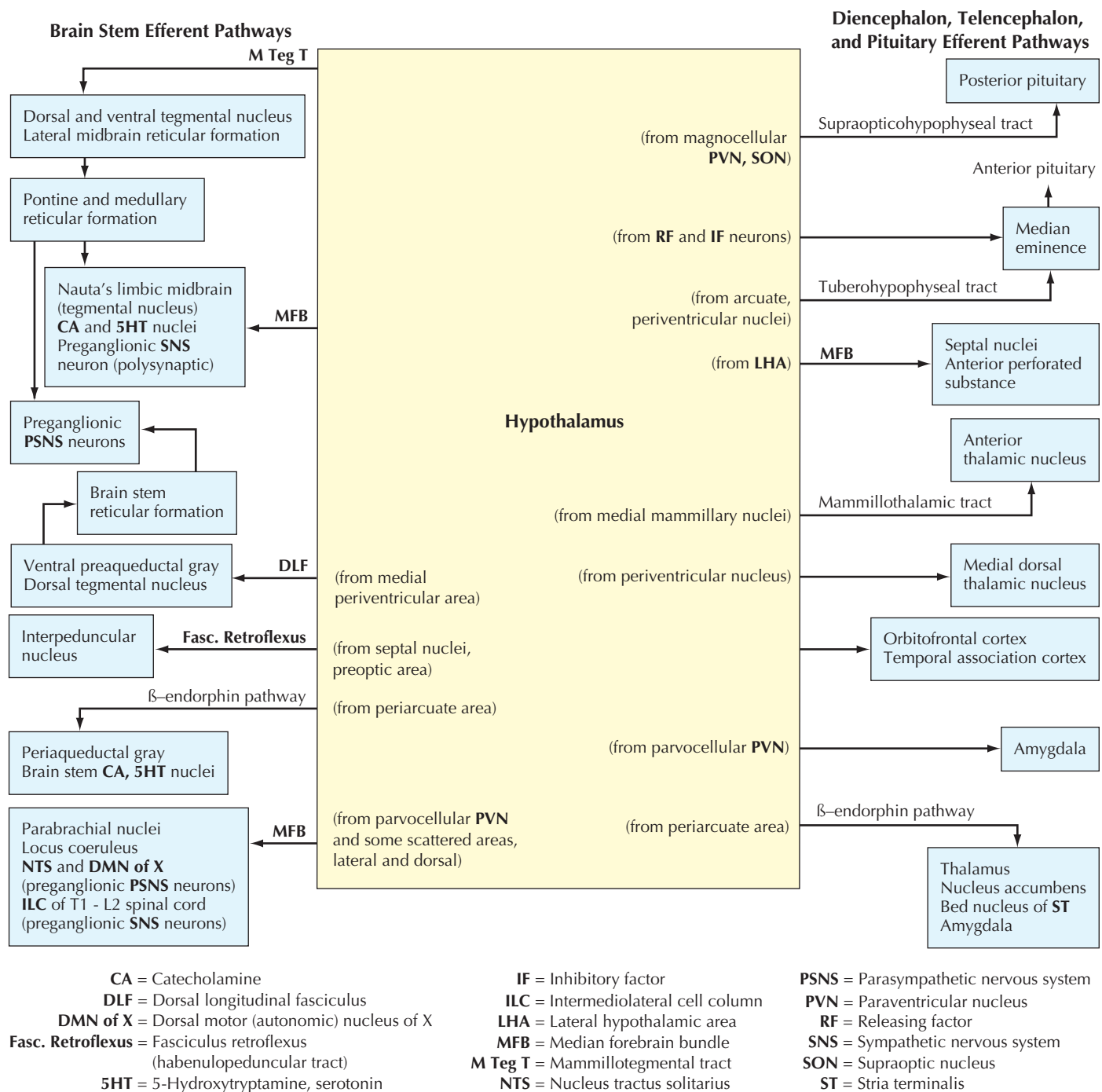




## 16.9 SCHEMATIC DIAGRAM OF MAJOR HYPOTHALAMIC AFFERENT PATHWAYS

The hypothalamus receives extensive input from many regions of the CNS. Descending inputs arrive from limbic forebrain structures (hippocampal formation, subiculum, amygdaloid nuclei), the cerebral cortex (anterior cingulate, orbitofrontal, prefrontal), and the thalamus (medial dorsal). Ascending inputs arrive from extensive areas of the autonomic brain

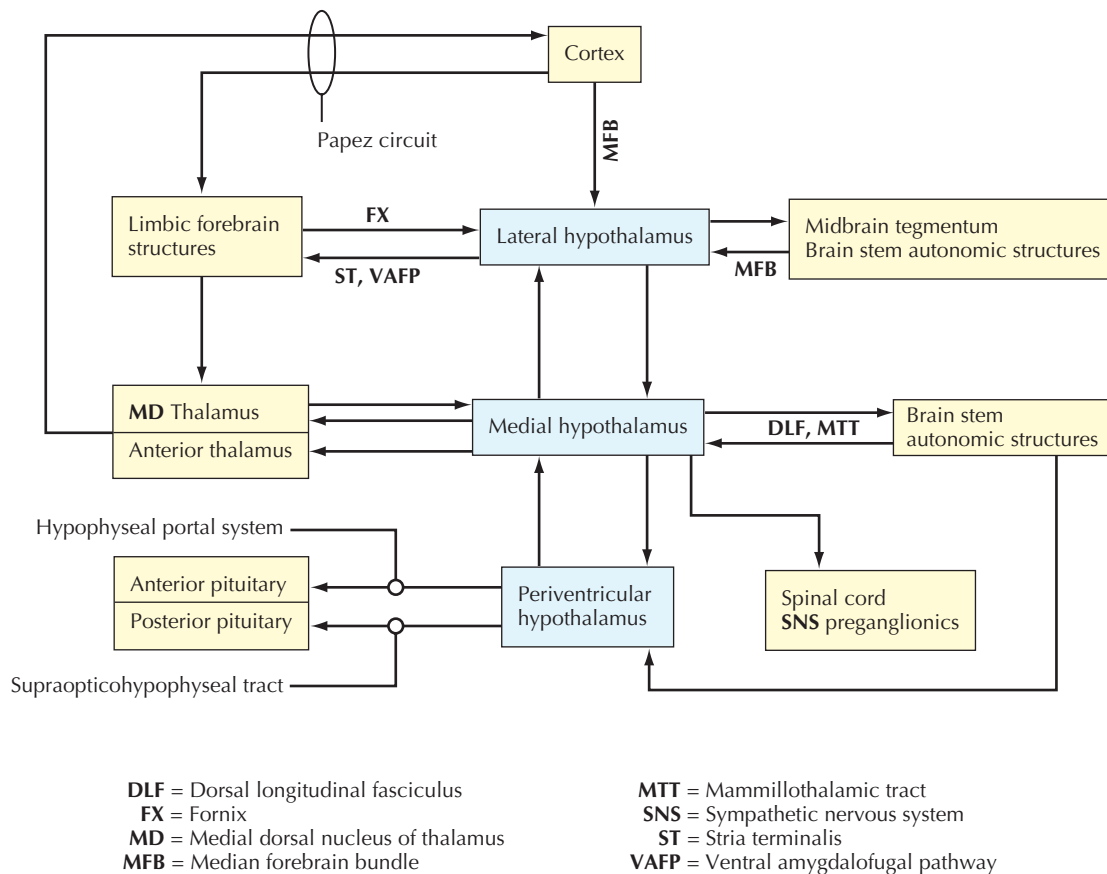
stem (tegmental nuclei, periaqueductal gray, parabrachial nuclei, nucleus tractus solitarius, locus coeruleus and tegmental catecholamine nuclei, raphe serotonergic nuclei) and from the brain stem reticular formation. The retina sends input directly to the suprachiasmatic nucleus, a nucleus of the hypothalamus that modulates diurnal rhythms. Blood-borne substances (cytokines, hormones, glucose, Na<sup>+</sup>, others) influence the hypothalamus via numerous routes and mechanisms.



## 16.10 SCHEMATIC DIAGRAM OF MAJOR HYPOTHALAMIC EFFERENT PATHWAYS

The hypothalamus gives rise to extensive efferent projections to many regions of the CNS. Ascending efferents are sent to limbic forebrain structures (amygdaloid nuclei, septal nuclei, the anterior perforated substance), the cerebral cortex (orbitofrontal cortex and temporal association cortex), and the thalamus (medial dorsal, anterior). Extensive projections are sent to the median eminence (releasing and inhibitory factors for control of anterior pituitary hormones, dopamine projections from the arcuate nucleus and periventricular nucleus)

and to the posterior pituitary. Additional efferent projections are sent directly and indirectly to the preganglionic neurons of the sympathetic and the parasympathetic nervous systems (median forebrain bundle, dorsal longitudinal fasciculus, mammillotegmental tract, and direct projections from the paraventricular nucleus); to widespread autonomic and visceral nuclei (noradrenergic neurons, serotonergic neurons, parabrachial nuclei, nucleus tractus solitarius, periaqueductal gray, tegmental nuclei, interpeduncular nucleus); and to the brain stem reticular formation.

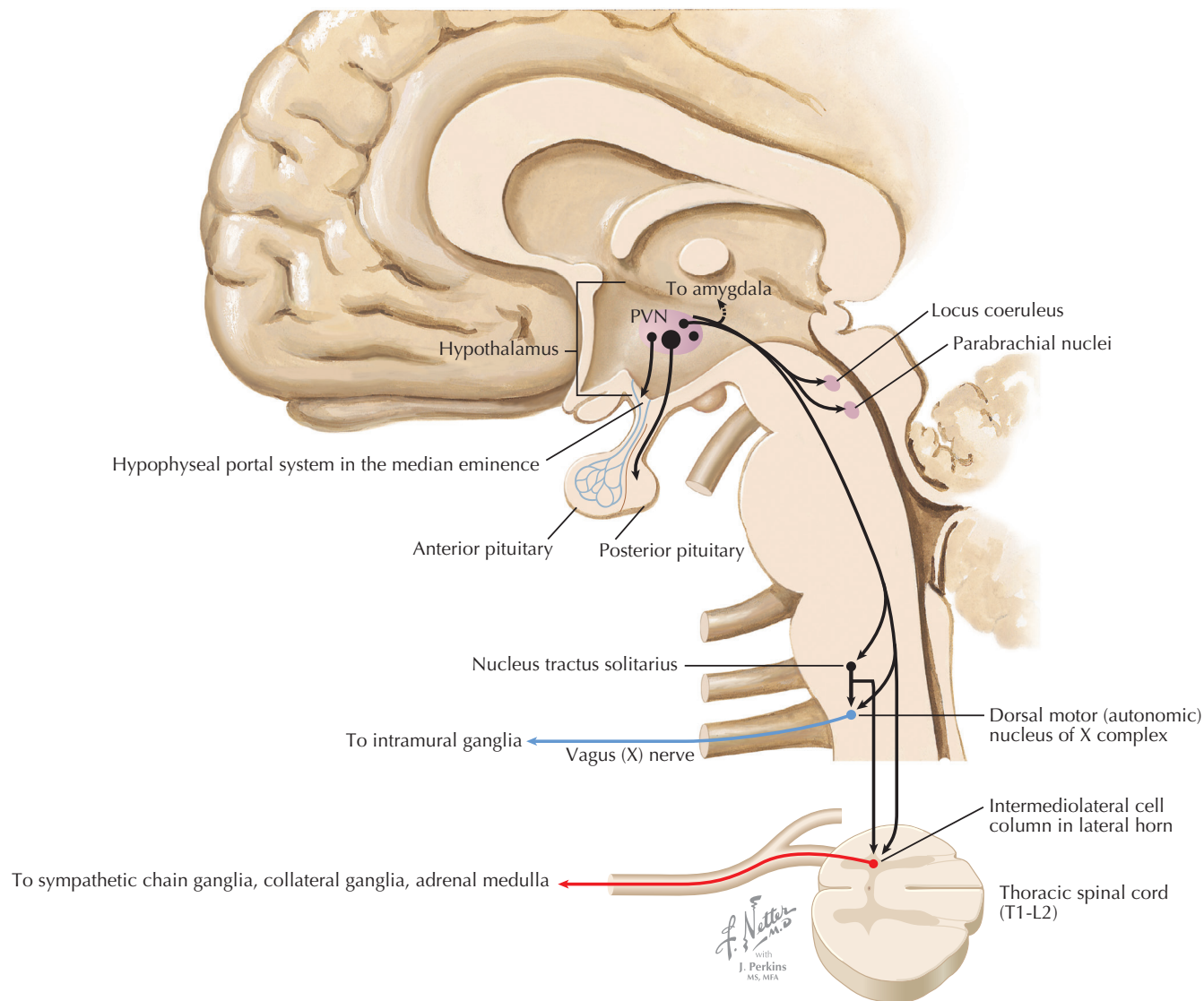


### 16.11 SUMMARY OF GENERAL HYPOTHALAMIC CONNECTIONS

The lateral, medial, and periventricular zones of the hypothalamus have specific connections with the cerebral cortex, limbic forebrain structures, thalamus, and widespread areas of the brain stem. Extensive efferent projections of the hypo-

thalamus are directed toward regulation of preganglionic sympathetic and parasympathetic neurons and toward release and regulation of hormones of the anterior and posterior pituitary. The anterior pituitary hormones regulate hormonal secretion and functional activities of many target structures throughout the body.



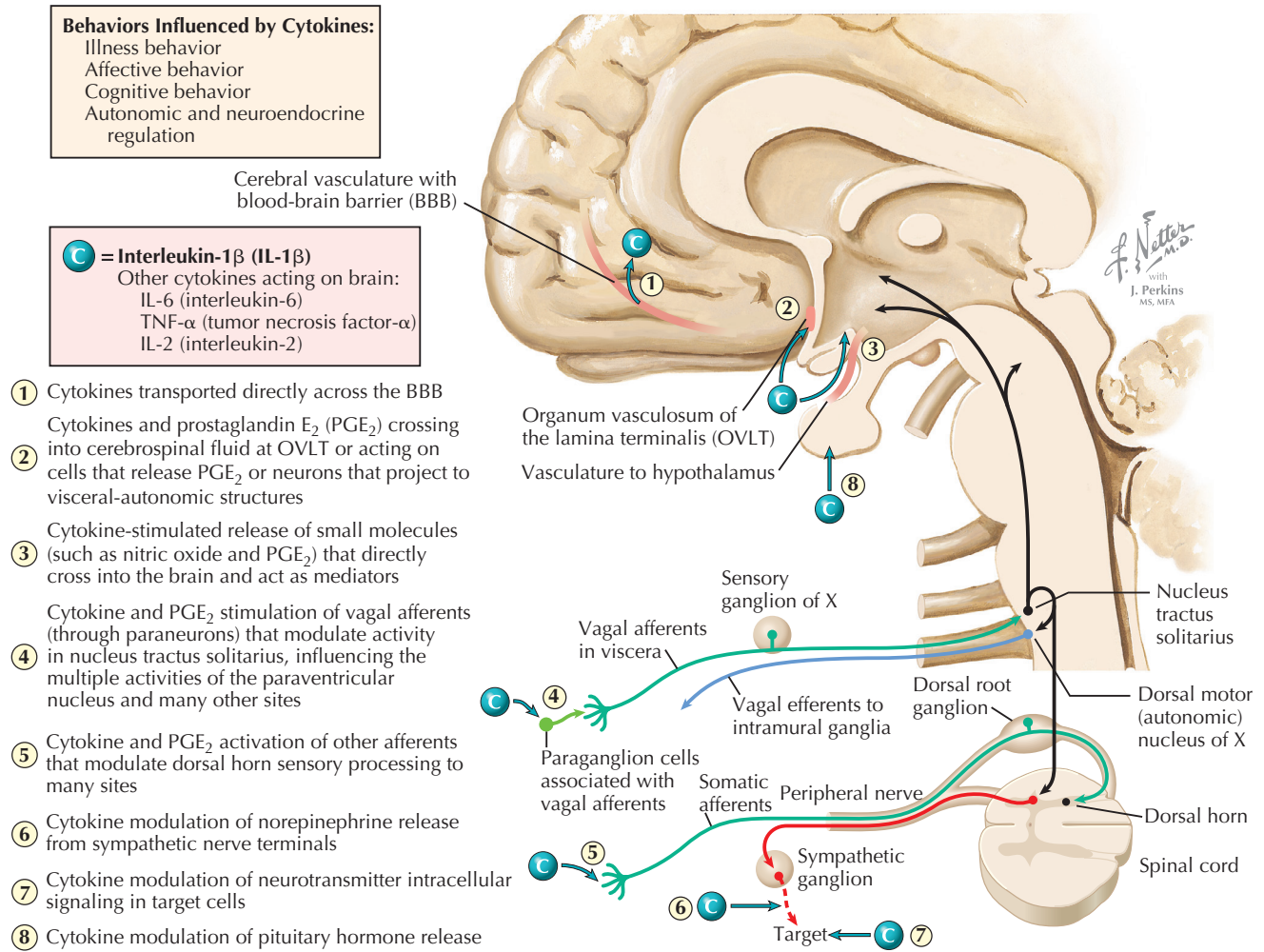


### 16.12 PARAVENTRICULAR NUCLEUS OF THE HYPOTHALAMUS: REGULATION OF PITUITARY NEUROHORMONAL OUTFLOW, AUTONOMIC PREGANGLIONIC OUTFLOW, AND LIMBIC ACTIVITY

The PVN has many projections that help to coordinate pituitary neurohormonal outflow, autonomic preganglionic outflow, and limbic activity. Magnocellular neurons send axons to the posterior pituitary, releasing oxytocin and vasopressin into the general circulation. Corticotropin-releasing factor (CRF) neurons and some vasopressin neurons send axons to the median eminence; these axons release their hormones into the hypophyseal portal system, influencing the release of ACTH. PVN parvocellular neurons send direct descending projections to preganglionic neurons for the parasympathetics (dorsal motor nucleus of CN X) and sympathetics (intermediolateral cell column in the T1–L2 lateral horn of the spinal cord) and to the nucleus tractus solitarius. PVN parvocellular neurons also send axons to several important limbic-related structures, such as the amygdaloid nuclei, parabrachial nuclei, and locus coeruleus.

#### CLINICAL POINT

The PVN of the hypothalamus is a small region along the upper borders of the third ventricle in the dorsal hypothalamus. It contains a remarkable array of chemically specific neural populations. The magnocellular neurons produce oxytocin and vasopressin along with neurophysins and project to the median eminence. Some parvocellular neurons synthesize corticotropin-releasing hormone and send axons to the contact zone of the median eminence, where corticotropin-releasing hormone is released into the hypophyseal portal vessels. Parvocellular neurons also send descending projections to the brain stem (particularly the nucleus solitarius) and the intermediolateral cell column of the thoracolumbar spinal cord, where activation of the SNS can occur. The PVN therefore can coordinate the activation of both the neuroendocrine components (hypothalamic-pituitary-adrenal axis and cortisol secretion) and the autonomic components (sympathetic activation, diminished parasympathetic activity) of a stress response or activational response. The PVN receives inputs from many limbic regions and from brain stem sites (parabrachial nuclei, brain stem noradrenergic nuclei, nucleus tractus solitarius) that provide visceral information to the PVN. In addition, the PVN receives a variety of inputs that help it to monitor inflammatory mediators (IL-1 $\beta$ , IL-6, tumor necrosis factor [TNF]- $\alpha$ , prostaglandin E<sub>2</sub> [PGE<sub>2</sub>]), and other small molecules (nitric oxide) that reflect the outside chemical milieu. This information is received through the hypothalamus and circumventricular organs, and some of it through the vagus nerve afferents and nucleus tractus solitarius. Thus, PVN is a key regulatory site for behavioral responses that require autonomic reactivity.

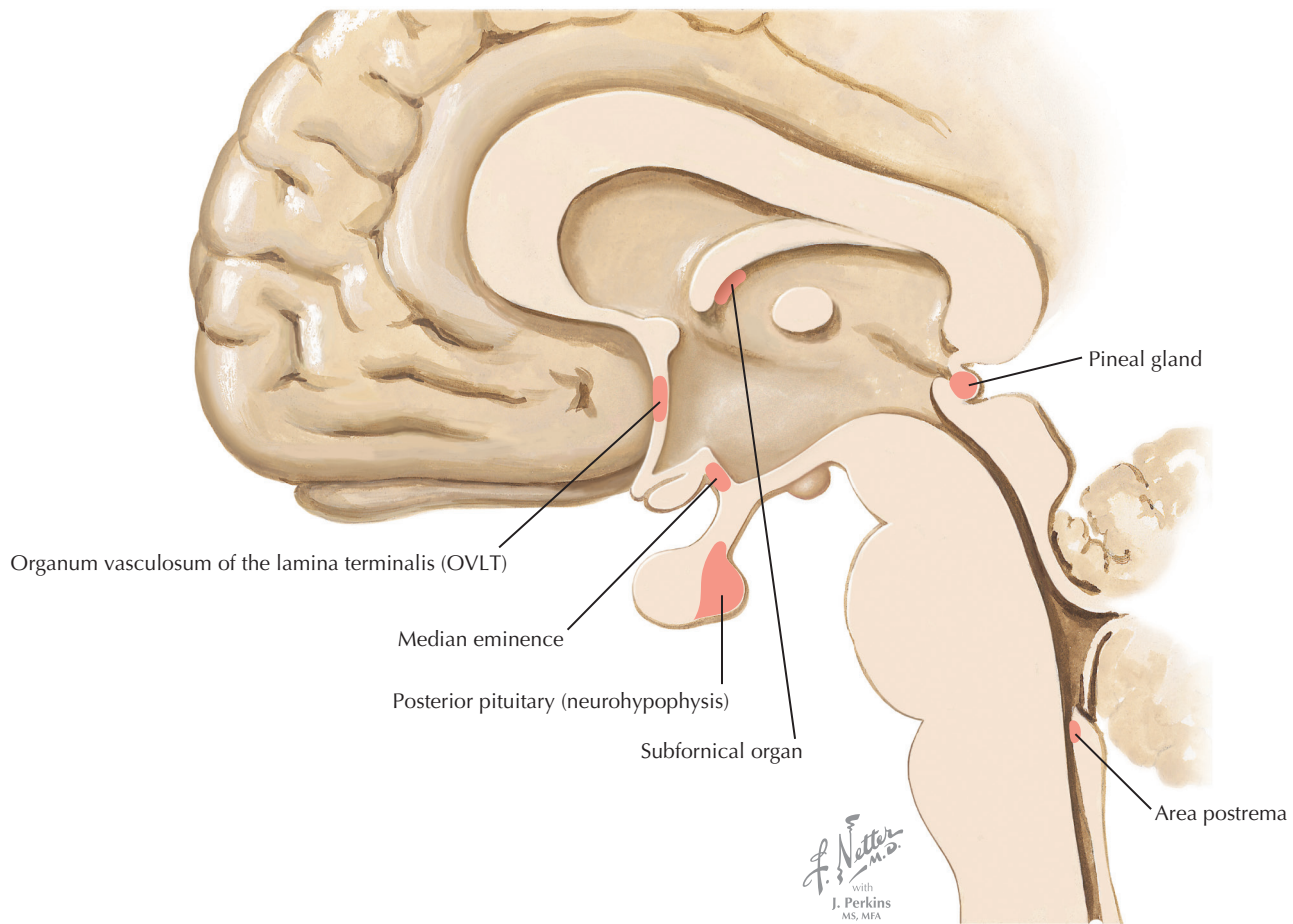


### 16.13 MECHANISMS OF CYTOKINE INFLUENCES ON THE HYPOTHALAMUS AND OTHER BRAIN REGIONS AND ON BEHAVIOR

Cytokines, including IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and IL-2, can influence central neuronal activity and behavior. This figure illustrates IL-1 $\beta$  access to the brain: (1) directly crossing the blood-brain barrier into the brain (especially in cortical regions); (2) acting on circumventricular organs (the OVLT) to release small mediators such as PGE<sub>2</sub>; (3) acting on vascular endothelial cells to release nitric oxide, which acts in the CNS; (4) activating vagal afferents that project into the nucleus tractus solitarius via paraganglion cells; and (5) activating other afferent nerve fibers. IL-1 $\beta$  can evoke illness behavior (fever, induction of slow-wave sleep, decreased appetite, lethargy, classical illness symptoms), can influence autonomic and neuroendocrine regulation, and can influence both affective and cognitive functions and behavior.

#### CLINICAL POINT

There is a widespread influence of cytokines, especially inflammatory cytokines (IL-1 $\beta$ , IL-6, TNF- $\alpha$ ), as well as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), on the nervous system. A key target of these influences is the PVN of the hypothalamus. Inflammatory cytokines can provoke a robust activation of cortisol secretion (through the hypothalamopituitary-adrenal axis) and SNS activation (via descending projections of the PVN). The consequences of prolonged stress activation include increased risk for many chronic diseases, such as cardiovascular disease and stroke, metabolic syndrome, type II diabetes, and many cancers. The cytokines can influence the PVN and other central neurons through several mechanisms, including some direct transport into the forebrain, actions on neurons of the OVLT that release PGE<sub>2</sub> and signal the PVN, release of nitric oxide and PGE<sub>2</sub> from vascular endothelial cells, and activation of vagal afferents and other afferents that send neural signals to PVN. Inflammatory cytokines also can stimulate the release of some hormones from pituitary cells, can alter neurotransmitter release in both the CNS and the autonomic nervous system (especially sympathetic norepinephrine), and can interact with neurotransmitter effects on target cells of autonomic innervation. Other cytokines such as IL-2 also appear to have central effects; the infusion of IL-2 in immunotherapy for some cancers was curtailed because of adverse effects of IL-2 on the brain, including depression and suicidal behavior.



### 16.14 CIRCUMVENTRICULAR ORGANS

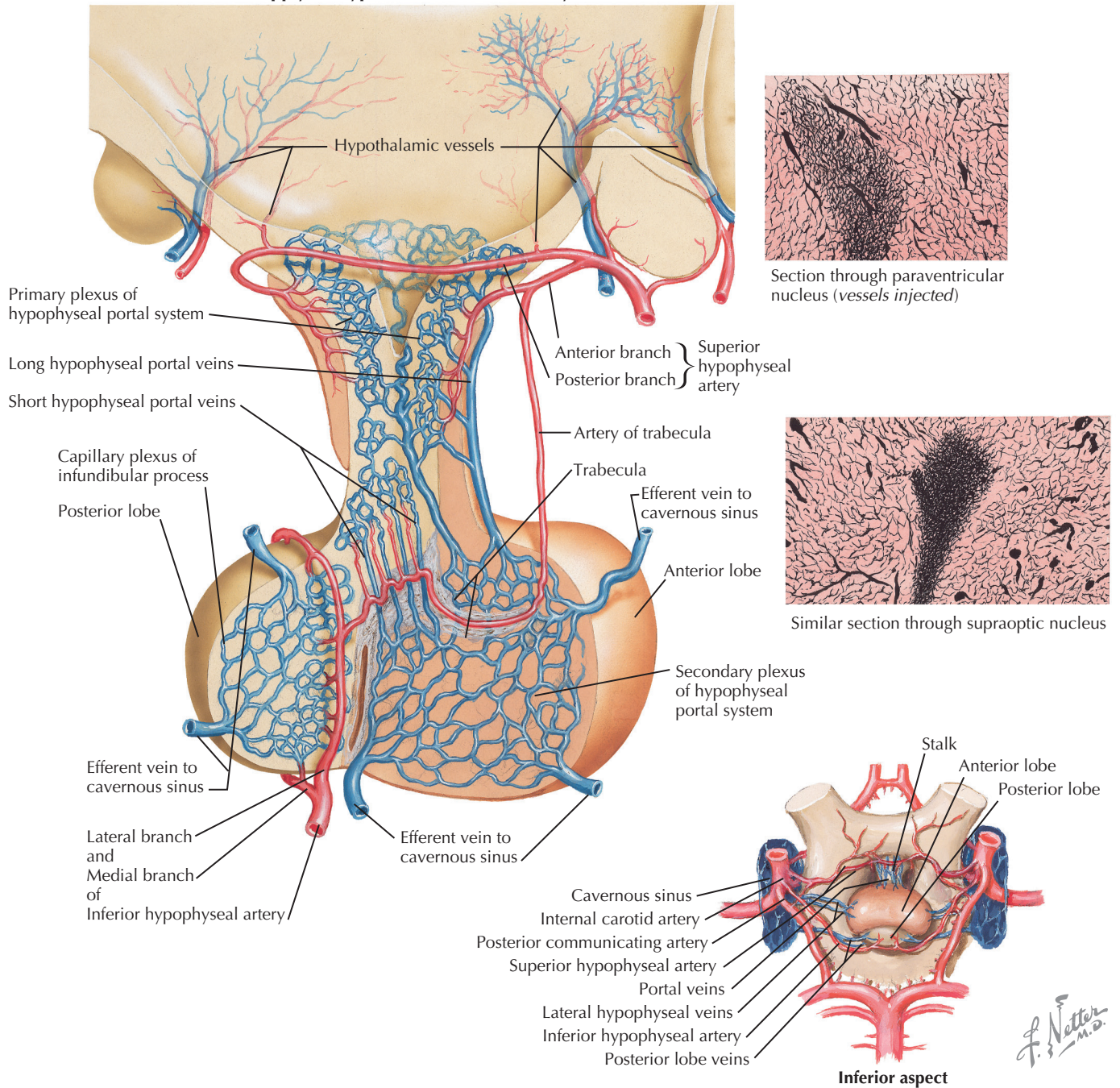
Circumventricular organs are “windows on the brain” that are devoid of the usual tight-junction endothelial appositions and instead have fenestrated vasculature. Thus, the circumventricular organs have no blood-brain barrier. Some of these organs (the OVLt, the subfornical organ, and the area postrema) have associated neurons that project to the hypothalamic and other visceral structures. They also have cells that can release small molecules such as  $\text{PGE}_2$  into the cerebrospinal fluid, thus affecting target structures at a distance. The neurohypophysis is a site of axonal release (from PVN and SON magnocellular neurons) of oxytocin and arginine vasopressin into the general circulation. The median eminence is a zone of neuroendocrine transduction for the secretion of releasing factors and inhibitory factors into the hypophyseal portal vasculature; these factors influence the release of anterior pituitary hormones. The pineal gland synthesizes and releases the hormone melatonin.

#### CLINICAL POINT

The CNS is protected from damage caused by many potentially harmful substances in the periphery by the blood-brain barrier. The CNS capillary endothelial cells contain tight junctions as well as specific transport mechanisms for the uptake of certain important substances (such as amino acids needed for neurotransmitter synthesis, glucose). Brain capillaries also can actively pump some substances out of the brain. Some regions of the brain contain fenestrated capillaries, and this permits the sampling of circulating substances. These are the circumventricular organs. The area postrema contains neurons that project to the nucleus tractus solitarius and activate the vomiting reflex. The subfornical organ contains neurons that respond to salt content in the blood and elicit protective neuroendocrine responses. The OVLt contains neurons that help to regulate blood pressure through an angiotensin II mechanism; these neurons also regulate  $\text{PGE}_2$  availability to the PVN and other central areas to influence activation of the hypothalamo-pituitary-adrenal axis and the SNS. The OVLt and subfornical organ also respond to pyrogens and help to regulate hypothalamic responses for control of body temperature. At the median eminence, circulating hormones and other substances can interact with the projecting axonal terminals that secrete releasing hormones and inhibitory hormones at the contact zone for regulation of anterior pituitary hormonal secretion. The posterior pituitary and the pineal gland also have fenestrated capillaries, enabling their secretion of hormones directly into the systemic circulation.



### Blood Supply of Hypothalamus and Pituitary Gland

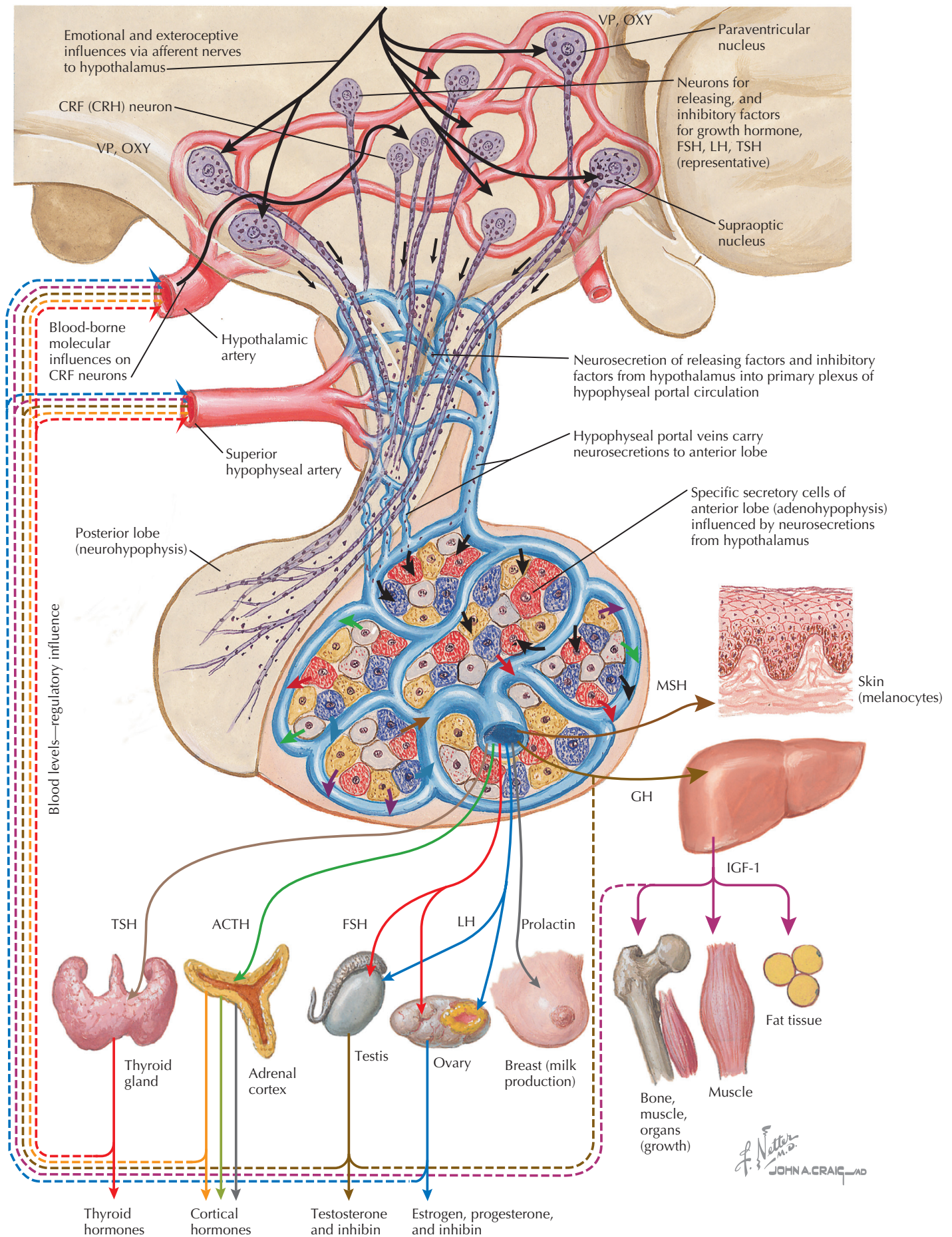


### 16.15 THE HYPOPHYSEAL PORTAL VASCULATURE

The hypophyseal portal vascular system derives from arterioles coming into the median eminence at the base of the hypothalamus. The primary capillary plexus is a site where releasing and inhibitory factors that influence the secretion of anterior pituitary hormones are released from axons (neuro-

crine secretion) whose neurons reside in the hypothalamus and other CNS sites. These releasing and inhibitory factors then travel through venules into the secondary capillary plexus in very high concentrations and act directly on anterior pituitary cells that synthesize and secrete the hormones of the anterior pituitary.





**Regulation of Anterior Pituitary Hormone Secretion**

### 16.16 REGULATION OF ANTERIOR PITUITARY HORMONE SECRETION

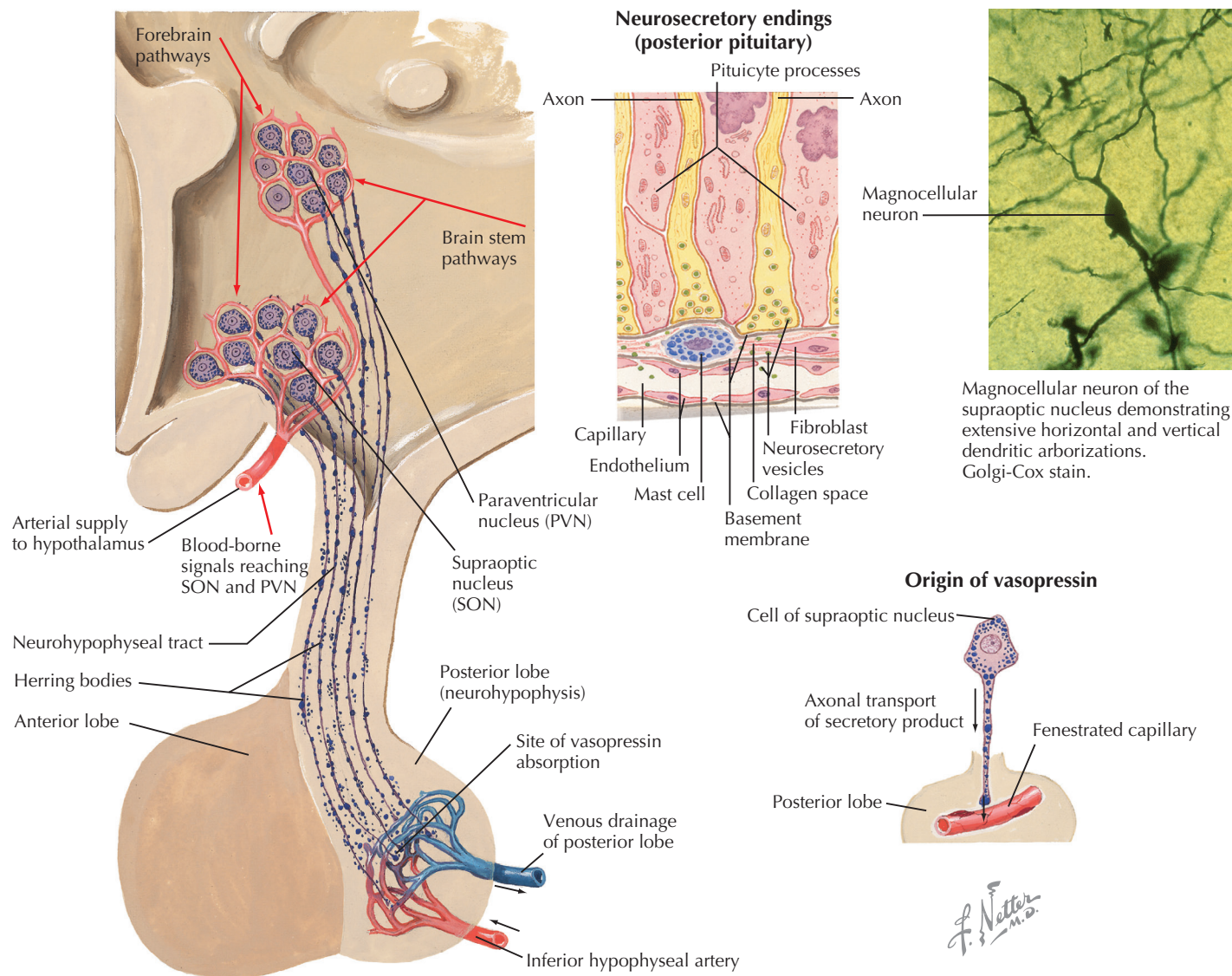
Neurons that synthesize releasing and inhibitory factors for control of anterior pituitary hormones send axons that terminate on the primary plexus of the hypophyseal portal system (the zone of neuroendocrine transduction) and release these factors into the hypophyseal portal blood. These factors then flow into the secondary hypophyseal portal plexus and regulate the release of anterior pituitary hormones. The major anterior pituitary hormones are thyroid-stimulating hormone (TSH), adrenal corticotrophic hormone (ACTH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (LTH), growth hormone (GH), and melanocyte-stimulating hormone (MSH). These anterior pituitary hormones act on peripheral target organs to effect release of target organ hormones or to influence metabolic and functional activities. For example, CRF neurons release CRF (CRH, corticotropin-releasing hormone) into the hypophyseal portal blood, regulating the release of ACTH, which in turn regulates the release of cortisol from the adrenal cortex. Magnocellular neurons of the PVN and SON send axons directly to the posterior pituitary and release oxytocin and arginine vasopressin directly into the systemic circulation.

#### CLINICAL POINT

The term *hypopituitarism* refers to the deficiency or absence of one or more anterior pituitary hormones. The process of pituitary dysfunction can be very slow in onset because of the great reserve; more than 75% of the anterior pituitary must be destroyed before symptoms become evident. Pituitary damage may result from tumors, ischemia and infarction, infiltrative lesions (e.g., sarcoidosis), head injury, immunological damage during pregnancy, or other causes. With some tumors such as pituitary adenomas initial symptoms may occur because of disruption of releasing hormones, such as gonadotropin releasing hormone (GnRH), leading to elevated secretion of prolactin, FSH, LH, and ACTH and cortisol, producing gonadal dysfunction. With progressive pituitary insufficiency, the first hormones to markedly fall generally are growth hormone (GH), which is highly conspicuous in children whose growth is impaired, and gonadotropins, causing amenorrhea in women and impotence or sexual dysfunction in men. At a later stage, impairment of TSH, ACTH, prolactin, and other hormones occurs; hormonal replacement therapy is necessary. Diabetes insipidus caused by posterior pituitary damage also may accompany pituitary insufficiency.

Many pituitary tumors secrete anterior pituitary hormones, leading to symptoms of pituitary hypersecretion. Prolactinomas (adenomas) result in excess prolactin secretion, gonadal dysfunction, and galactorrhea. GH-secreting adenomas result in gigantism if they are present before the epiphyseal plates of the long bones are closed and in acromegaly in adults, with soft tissue enlargement, enlarged hands and feet, and coarse facial features. ACTH-secreting adenomas lead to Cushing's disease. Pituitary tumors commonly impinge on the optic chiasm and produce bitemporal visual field defects (bitemporal hemianopia), usually starting in the upper outer fields.





### 16.17 POSTERIOR PITUITARY (NEUROHYPOPHYSEAL) HORMONES: OXYTOCIN AND VASOPRESSIN

Magnocellular neurons in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) send axons directly through the infundibular region and the pituitary stalk to terminate on the vasculature in the posterior pituitary. Neurons from both nuclei synthesize and release oxytocin and arginine vasopressin into the systemic vasculature. Brain stem and forebrain pathways terminate on the magnocellular neurons and regulate their secretion of oxytocin and vasopressin. These magnocellular neurons possess extensive protein synthesis capacity and transport the vesicles in which their hormones are packaged to the axon terminals with very fast axoplasmic transport. The hormones are released from the terminals and diffuse through the fenestrated capillaries directly into the systemic vasculature (see inset of neurosecretory efferent endings from magnocellular neurons in PVN and SON).

#### CLINICAL POINT

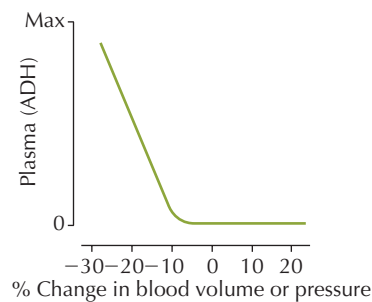
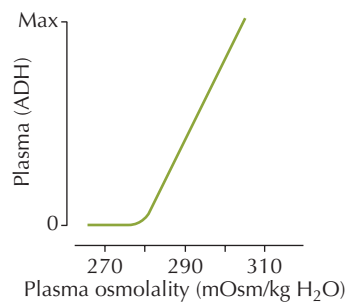
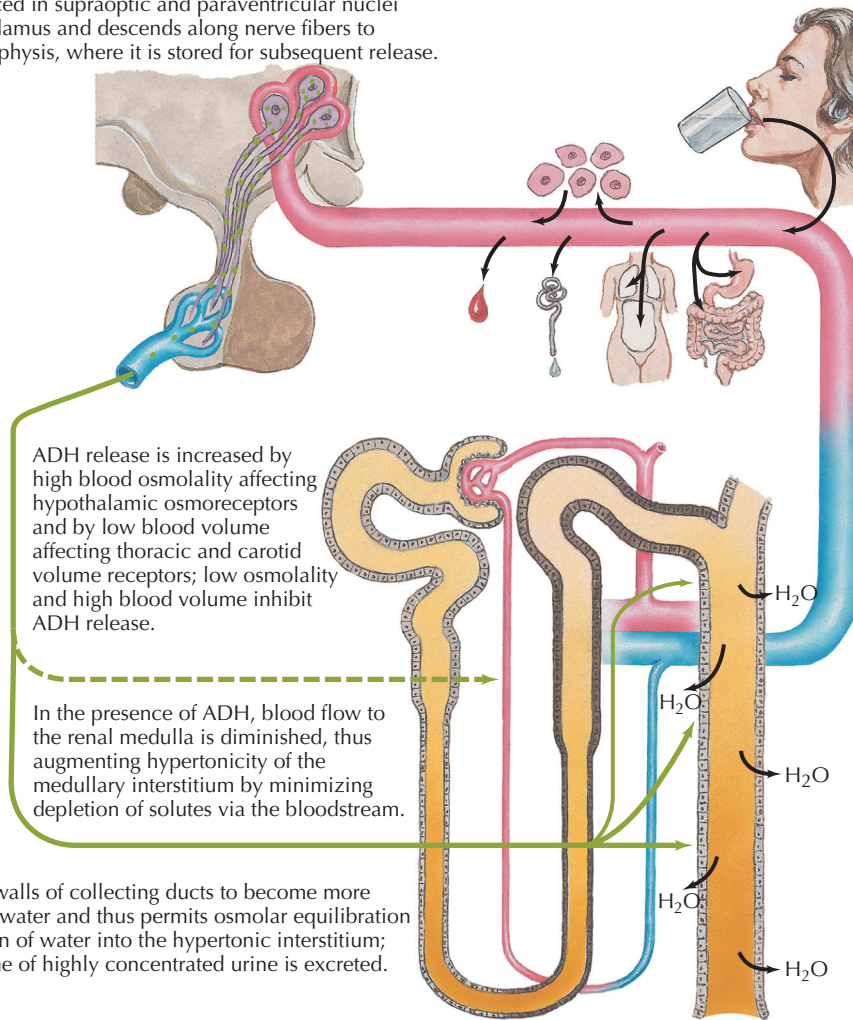
The SON and magnocellular neurons of the PVN of the hypothalamus synthesize and secrete both oxytocin and arginine vasopressin

(antidiuretic hormone, or ADH), along with their neurophysin carrier proteins. A majority of vasopressin comes from the SON, and a majority of oxytocin comes from magnocellular PVN. These neuronal groups send axons (the supraopticohypophyseal tract) into the posterior pituitary, where they terminate on fenestrated capillaries and secrete their hormones directly into the systemic circulation. These neurons are called neuroendocrine transducer cells. Oxytocin cells respond to estrogen and to afferent signals caused by suckling, and they stimulate milk let-down (milk ejection reflex) and uterine contraction in pregnancy. Vasopressin neurons respond to changes in blood osmolarity, secreting vasopressin in the presence of high osmolarity. This causes the collecting tubules in the kidney to increase water resorption and prevent diuresis. If the supraopticohypophyseal tract or associated neurons (seen in congenital disorders) are damaged, as happens with pituitary stalk sectioning, diabetes insipidus results. Diabetes insipidus involves the loss of vasopressin secretion and the production of huge amounts (10+ liters per day) of dilute urine, provoking marked polydipsia. Vasopressin replacement therapy is necessary. Alcohol consumption, some antiseizure drugs (phenytoin), and anticholinergic agents may also inhibit vasopressin secretion. Excessive vasopressin secretion (called inappropriate secretion of ADH, or SIADH) may occur because of partial damage to the hypothalamus, a vasopressin-secreting tumor in the periphery (e.g., lung carcinoma), or as the result of treatment by chemotherapeutic and other pharmacological agents. SIADH results in hypo-osmolar serum, hyponatremia, and high urine osmolarity.

### Mechanism of Antidiuretic Hormone in Regulating Urine Volume and Concentration

ADH is produced in supraoptic and paraventricular nuclei of the hypothalamus and descends along nerve fibers to the neurohypophysis, where it is stored for subsequent release.

Blood osmolality and volume are modified by fluid intake (oral or parenteral); water and electrolyte exchange with tissues, normal or pathological (edema); loss via gut (vomiting, diarrhea); loss into body cavities (ascites, effusion); or loss externally (hemorrhage, sweat).



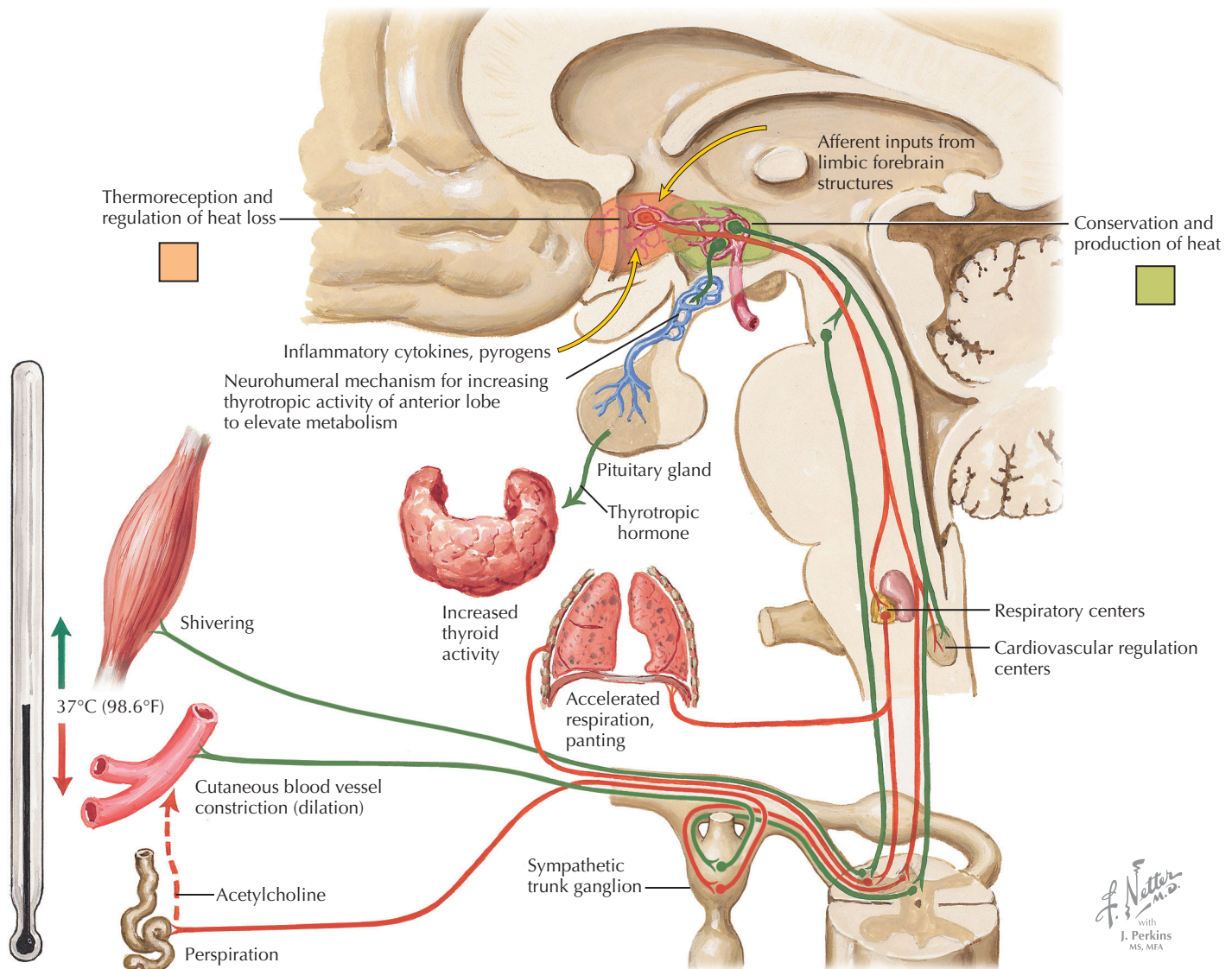
*F. Netter M.D.*

### 16.18 VASOPRESSIN (ANTIDIURETIC HORMONE) REGULATION OF WATER BALANCE AND FLUID OSMOLALITY

Vasopressin regulates the volume of water secreted by the kidneys. Its secretion is regulated by the osmolality of body fluids and by blood volume and pressure. Changes in body fluid osmolality of a small percentage are sufficient to significantly alter vasopressin secretion. Decreases in blood volume

and pressure of 10% to 15% or more are needed to affect vasopressin secretion. The blood volume and pressure sensors are found in the large pulmonary vessels, the carotid sinus, and the aortic arch. These baroreceptors respond to the stretching of the vessel wall, which is dependent on blood volume and pressure. The figure shows the mechanisms of action of vasopressin on the kidney, with resultant effects on urine volume and concentration.





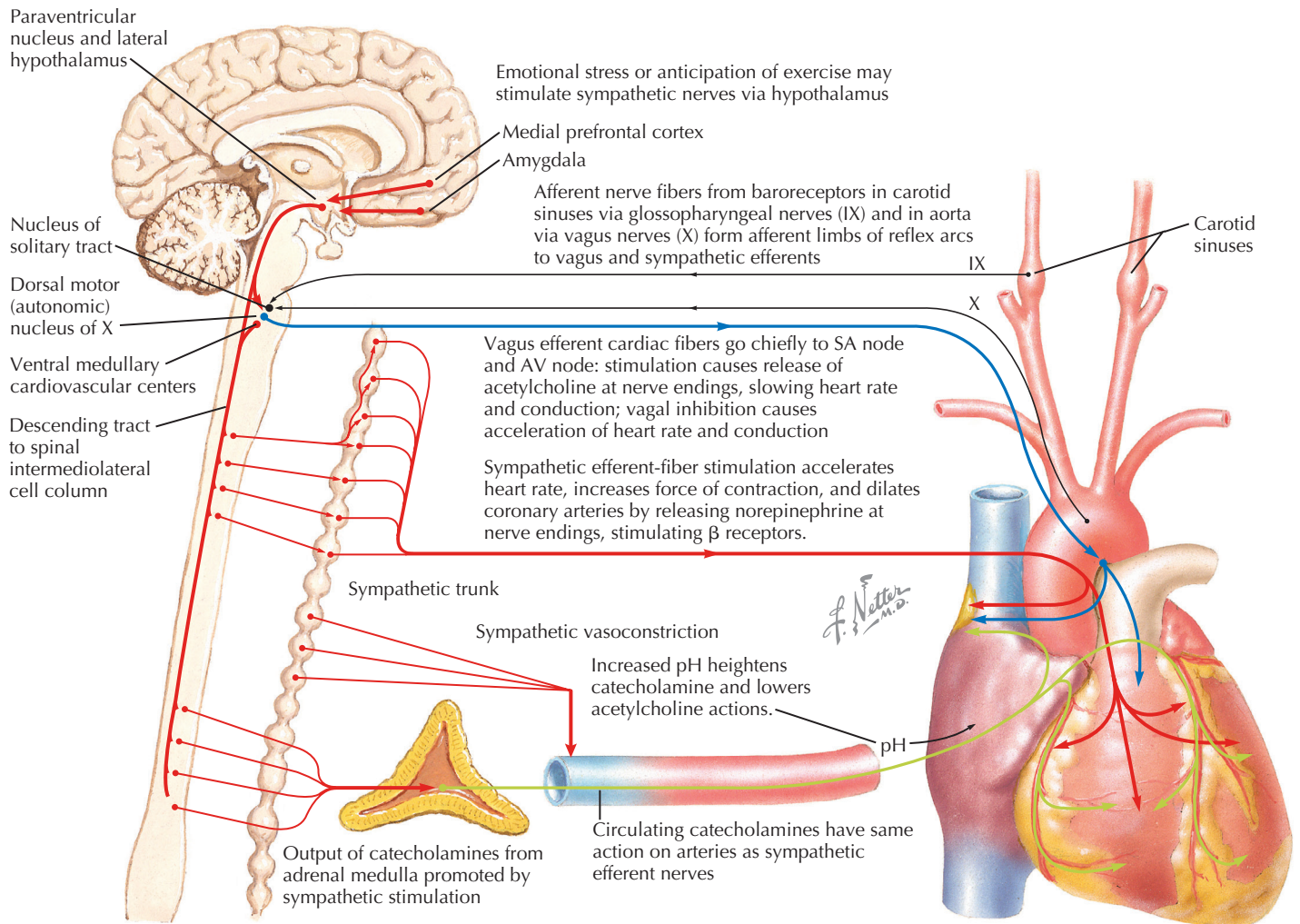
*F. Netter M.D.*  
with  
J. Perkins  
MS, MFA

### 16.19 THE HYPOTHALAMUS AND THERMOREGULATION

The preoptic area of the hypothalamus contains heat-sensitive neurons, and the posterior hypothalamic area contains cold-sensitive neurons. The preoptic area and the anterior hypothalamic area initiate neuronal responses for heat dissipation (parasympathetic); the posterior hypothalamic area initiates neuronal responses for heat generation (sympathetic). Neuronal pathways arising from the brain stem and limbic forebrain areas can modulate the activity of these thermoregulatory

systems. The preoptic area is responsive to pyrogens and the inflammatory cytokine IL-1 $\beta$ ; this area can generate an increased set point for temperature regulation, thus initiating a disease-associated fever. Extensive hypothalamic connections with the brain stem and spinal cord are used to initiate appropriate heat-dissipation or heat-generation responses. Appropriate behavioral responses also are initiated to optimize thermoregulation (e.g., going to a warmer or cooler location).





## 16.20 HYPOTHALAMIC REGULATION OF CARDIAC FUNCTION

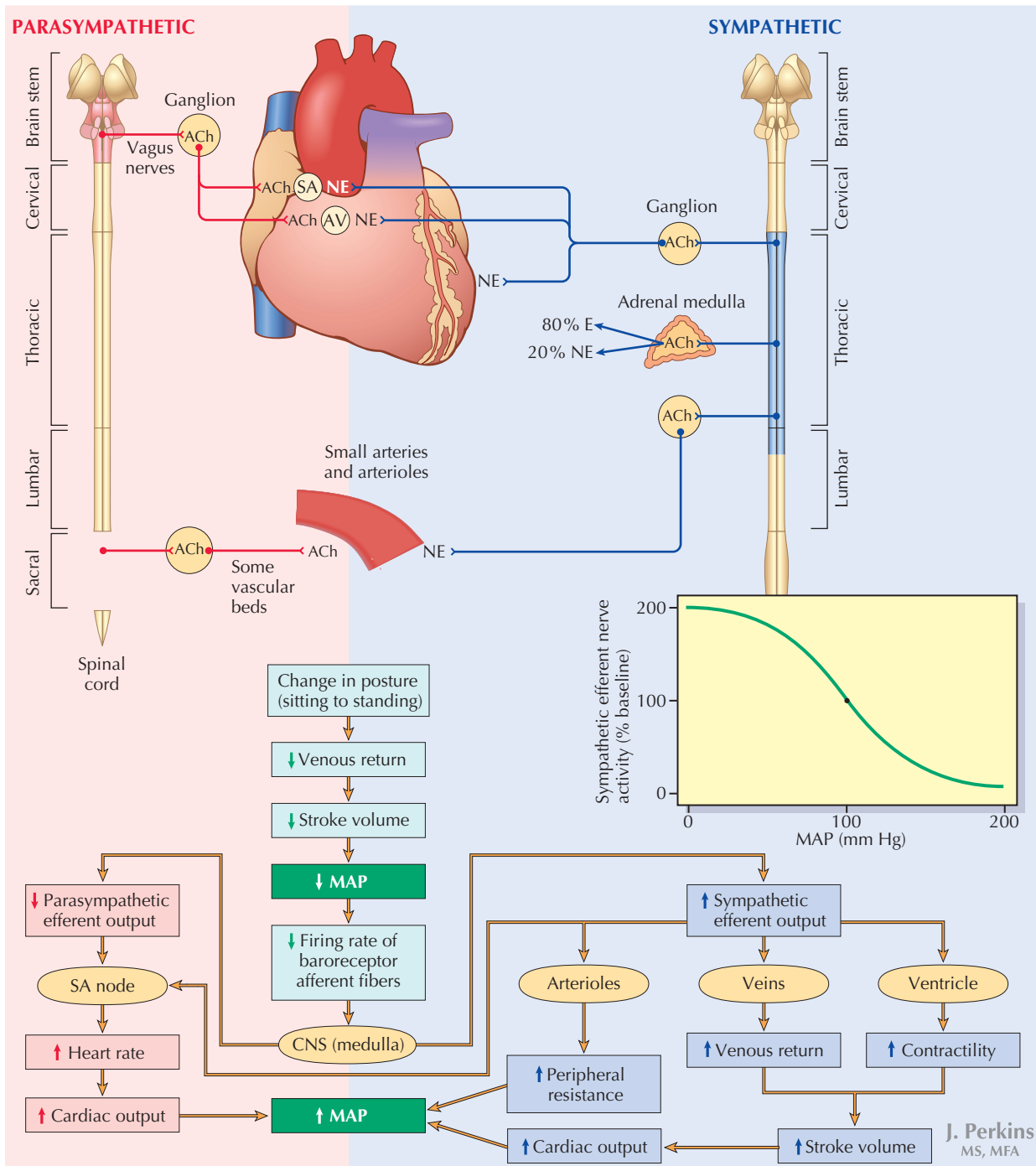
Regulation of cardiovascular (CV) function by the brain involves several domains of neuronal control. In the forebrain, medial prefrontal cortex, limbic cortical areas, and amygdaloid nuclei mediate emotional and behavioral responses and influence cardiovascular function. These forebrain areas act through projections to the hypothalamus (lateral hypothalamic area, paraventricular nucleus, preoptic and anterior hypothalamic areas for parasympathetic control, and the posterior hypothalamic area for sympathetic control).

These hypothalamic regulatory regions send projections to many brain stem sites, including the parabrachial nuclei, ventral medullary cardiovascular centers, nucleus solitarius,

the dorsal motor (autonomic) nucleus or X, and the intermediolateral cell column of the thoracic spinal cord lateral horn.

The parabrachial nuclei also respond to visceral afferent input and nociceptive input to regulate CV responses to pain, respiratory challenges, and gastrointestinal activity. The ventromedial CV medullary area generates CV responses needed for thermogenesis, and the ventrolateral CV medullary area helps to maintain blood pressure and CV responses during an upright posture and is responsive to baroreceptor reflexes.

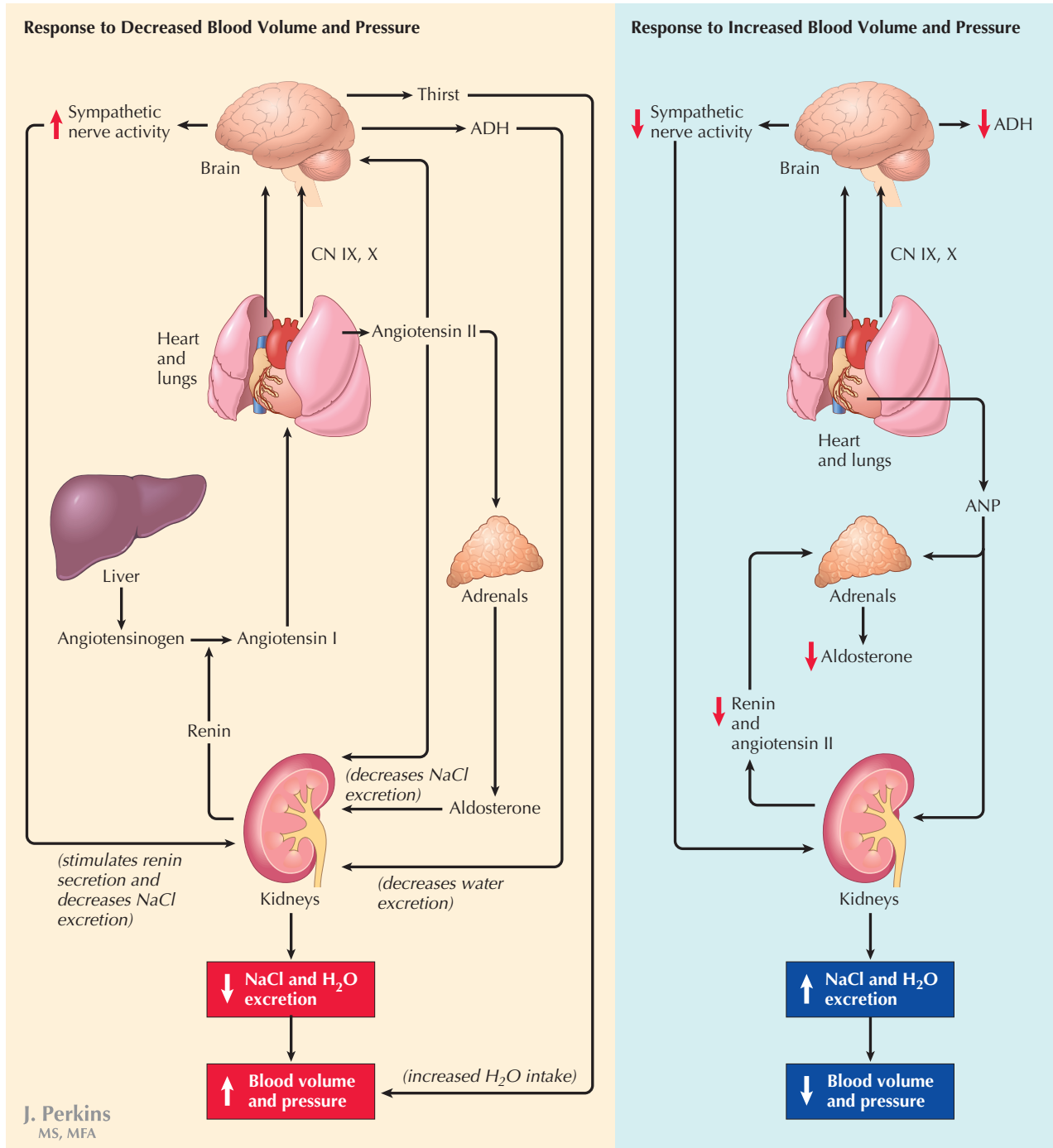
The nucleus solitarius is a major integrative center for descending (limbic and hypothalamic), local brain stem, and ascending regulation of autonomic preganglionic responses (dorsal motor [autonomic] nucleus of X for parasympathetic, intermediolateral cell column for sympathetic).



### 16.21 SHORT-TERM REGULATION OF BLOOD PRESSURE

Both the sympathetic and parasympathetic divisions of the autonomic nervous system are involved in maintaining blood pressure on a second-by-second basis. Numerous descending pathways from the brain stem (including the nucleus tractus solitarius, tegmental catecholamine nuclei, locus coeruleus, raphe nuclei, rostral ventrolateral medulla and other medullary reticular regions, parabrachial nuclei, angiotensin II-containing neurons, and many other sites) and the hypo-

thalamus regulate the outflow of autonomic preganglionic neurons associated with short-term blood pressure regulation. The hypothalamus and the nucleus tractus solitarius are key sites integrating limbic forebrain and cortical influences over these brain stem regions that regulate blood pressure. The brain stem sites have extensive interconnections with each other. The example of blood pressure regulation in this figure is based on change in posture. (ACh, acetylcholine; AV, atrio-ventricular node; E, epinephrine; MAP, mean arterial pressure; NE, norepinephrine; SA, sinoatrial node.)

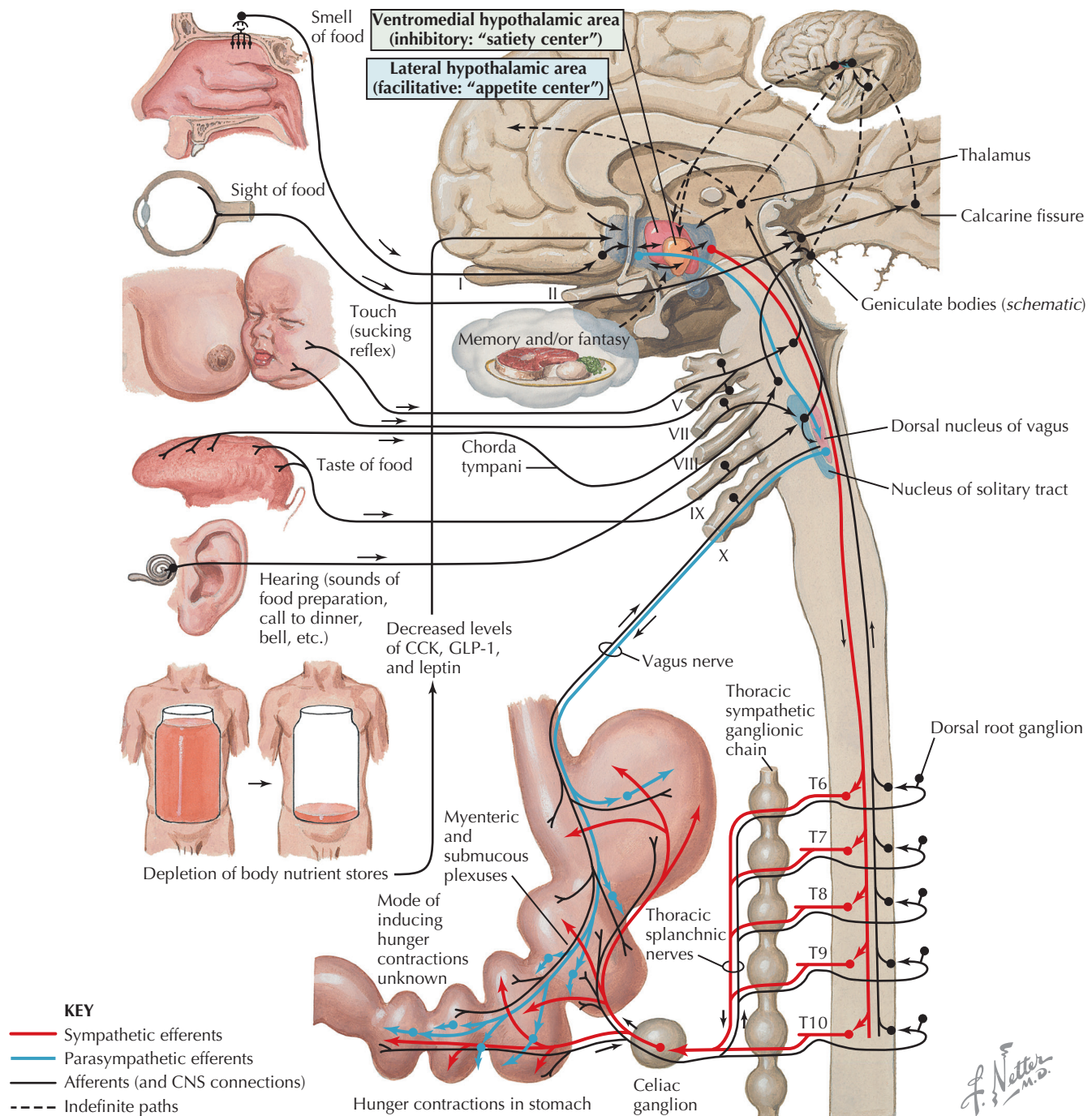


## 16.22 LONG-TERM REGULATION OF BLOOD PRESSURE

When blood volume and blood pressure change, the kidneys respond by either retaining NaCl and water or excreting NaCl and water in order to restore blood volume to its normal homeostatic state. With increased sympathetic activation,

norepinephrine and epinephrine secretion from sympathetic nerve terminals and the adrenal medulla increase in the circulation and act on the kidneys to reduce NaCl excretion. (ADH = antidiuretic hormone [also called vasopressin]; ANP = atrial natriuretic peptide.)

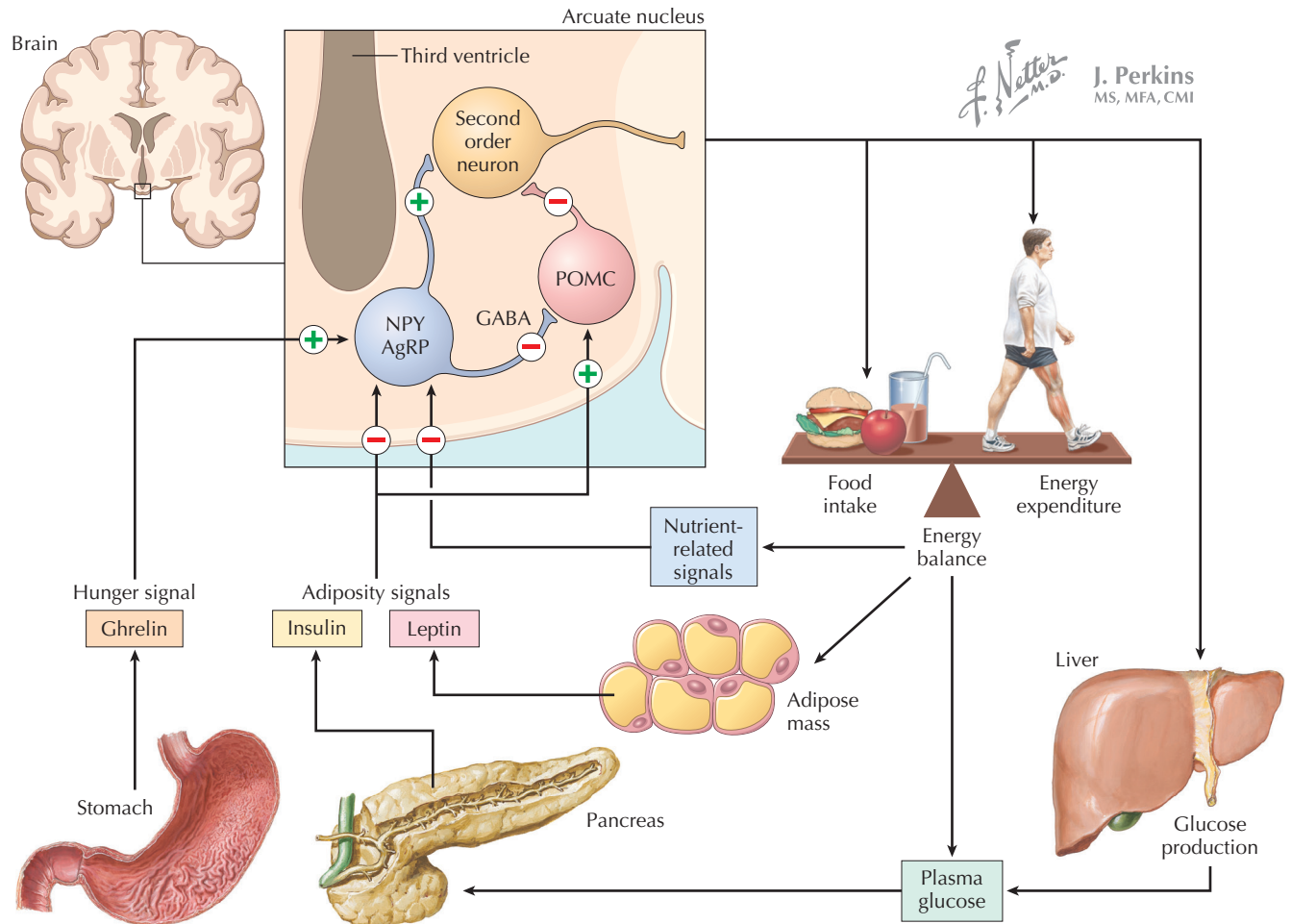




### 16.23 NEURAL CONTROL OF APPETITE AND HUNGER

The sensations of hunger and satiety are complex and include multiple neural pathways and circulating hormones. This figure depicts pathways involved in the sensation of hunger. Although our understanding is incomplete, the hypothalamus is known to play a critical role in controlling appetite and food intake. When food is ingested, cholecystikinin (CCK) and glucagon-like peptide (GLP-1) are released from neuroendocrine cells in the intestine. These hormones suppress appetite and give the sensation of satiety. In the absence of food, the

levels of these hormones are low. Long-term regulation of food intake involves the hormone leptin, which is produced by fat cells. When fat stores are high, leptin is released and appears to act on the hypothalamus to suppress appetite. When body nutrient stores are depleted, leptin levels are low. Other hormones such as ghrelin also are involved with control of hunger and satiety. Both the cerebral cortex and limbic forebrain structures have regulatory connections with this hypothalamic circuitry, permitting cognitive and emotional factors to influence appetite and eating behavior.



### 16.24 SIGNALING SYSTEMS INVOLVED IN REGULATION OF FOOD INTAKE, BODY WEIGHT, AND METABOLISM

The hypothalamus regulates food intake, body weight, and metabolism. The hormone ghrelin is produced by the gastric mucosa of the stomach when it is empty and stimulates cells in the arcuate nucleus of the hypothalamus to bring about increased food intake. The hormone leptin is made by white adipose tissue during robust metabolic activity and also acts on cells in the arcuate nucleus. High levels of ghrelin and low levels of leptin stimulate food intake, but high levels of leptin do not suppress eating activity.

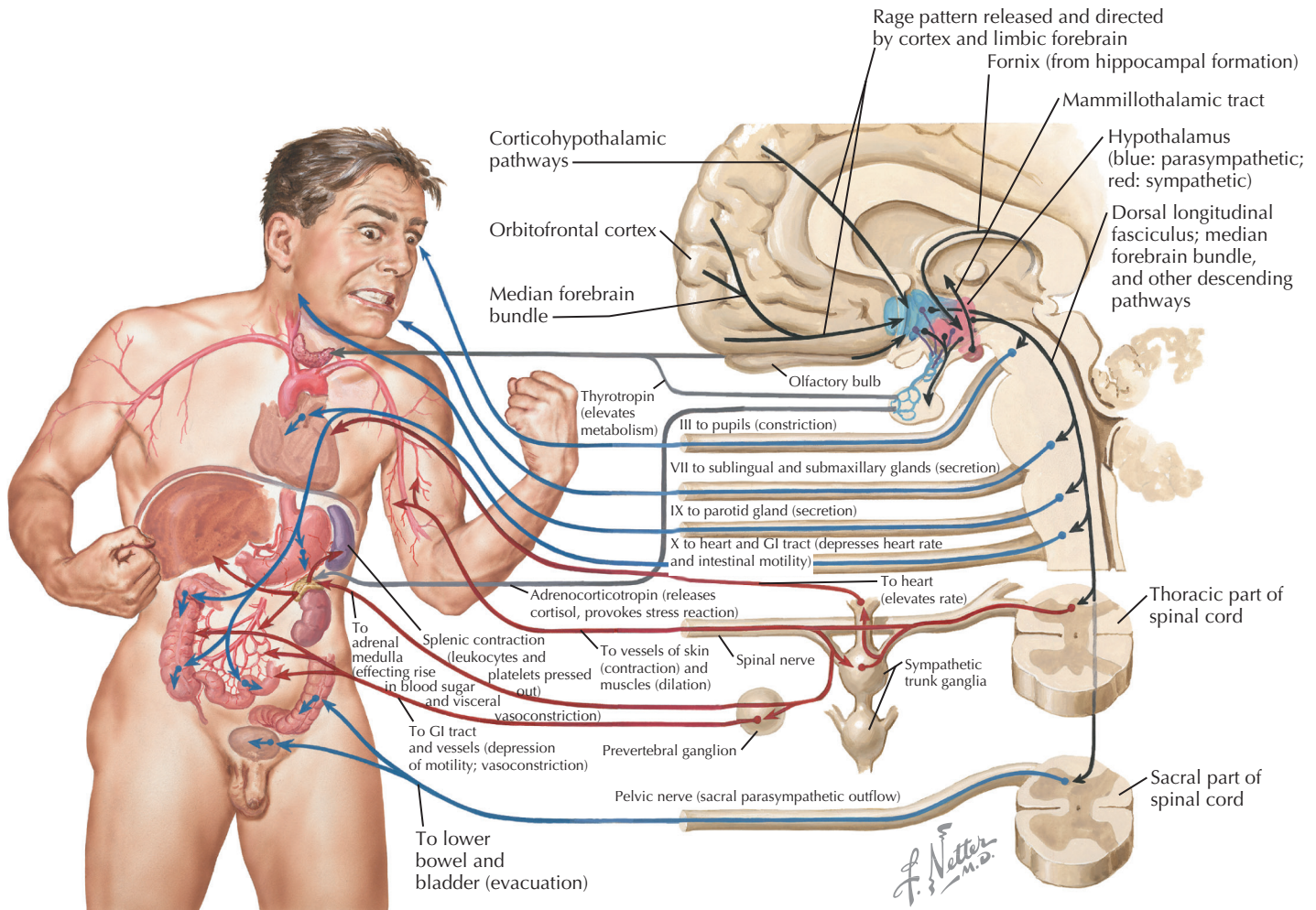
Ghrelin and leptin have access to the arcuate nucleus neurons through the hypophyseal portal vessels, which are devoid of a blood-brain barrier. These hormones act on cells of the arcuate nucleus that use neuropeptide Y (NPY) and agouti-related protein (AgRP) as neurotransmitters. These

arcuate neurons act through connections in the hypothalamus with the paraventricular nucleus, ventromedial nucleus, dorsomedial nucleus, and lateral hypothalamic area, and with descending connections with the parabrachial nuclei, and can activate feeding behavior.

Other neurons in the arcuate nucleus, using pro-opiomelanocortin (POMC) derivatives such as  $\alpha$ -melanocyte stimulating hormone and  $\beta$ -endorphin have connections with these same hypothalamic and brain stem targets and can suppress feeding behavior. Circadian-related circuits from the suprachiasmatic nucleus project to these same hypothalamic nuclei, superimposing circadian influences on feeding behavior.

Superimposed on this circuitry are limbic and cortical connections, including olfactory projections, which can provide emotional, behavioral, or volitional components to the control of food intake and appetite.

### Neural, Neuroendocrine and Systemic Components of Rage Reaction

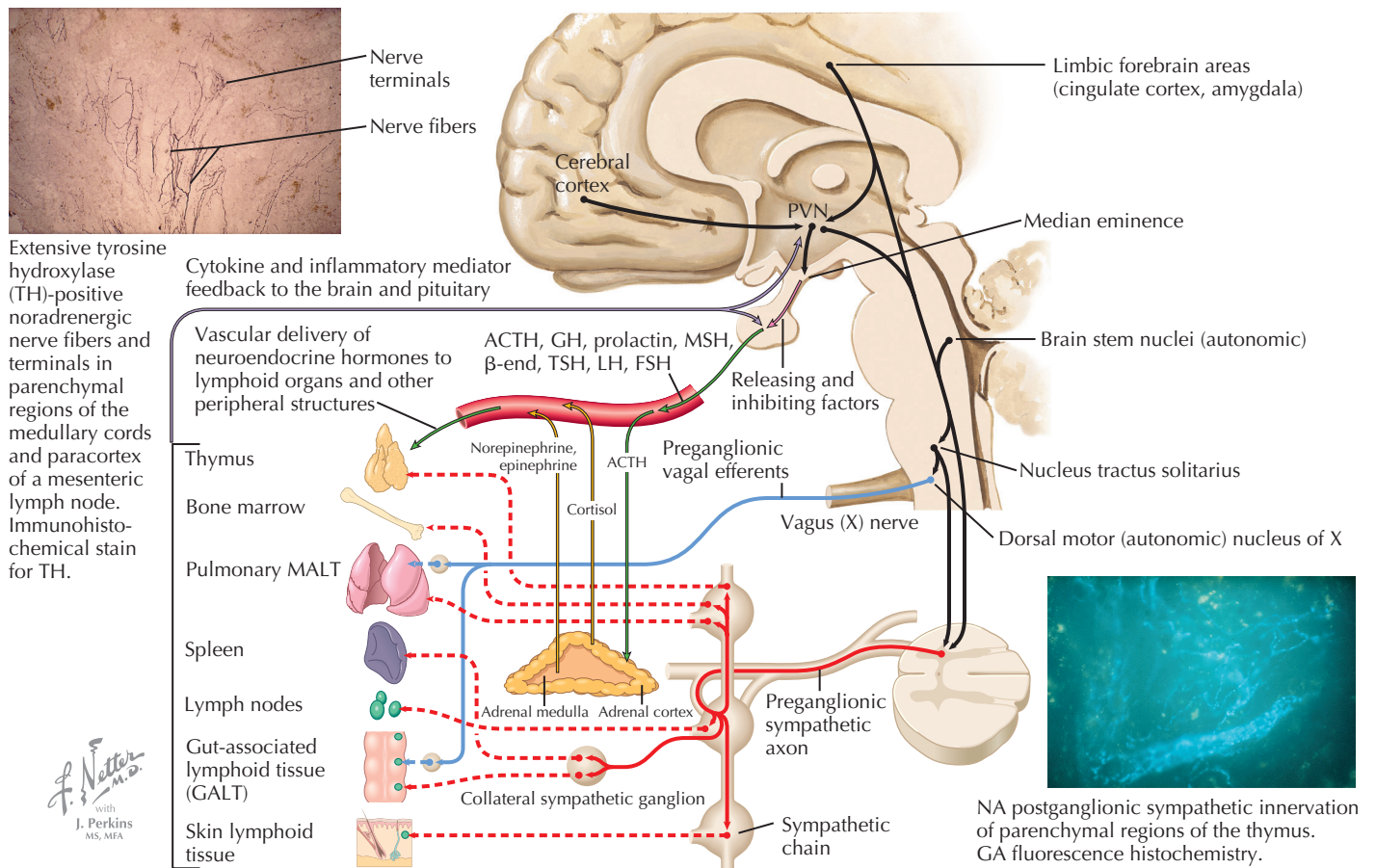


#### 16.25 NEURAL AND NEUROENDOCRINE ROLES IN THE FIGHT-OR-FLIGHT RESPONSE

The classic sympathetic fight-or-flight response, shown here as a rage response, involves the secretion of neuroendocrine “stress hormones,” including cortisol from the hypothalamo-pituitary-adrenal (HPA) axis and norepinephrine and epinephrine from sympathetic nerve terminals and the adrenal medulla. Sympathetic connections with the viscera initiate physiological changes to support the integrated fight-or-flight response. These changes include diversion of blood from the

viscera and skin to the muscles, increased heart rate and cardiac output and contractility, bronchodilation, pupillary dilation, decreased gastrointestinal activation, decreased renal activity, glycogenolysis from the liver with increased blood glucose for fuel, and many other actions. Inputs from limbic forebrain regions, the cerebral cortex, and the brain stem regulate the complex hypothalamic control of neuroendocrine and autonomic outflow and are key in initiating the classic fight-or-flight response. In this response, the brain stem parasympathetic neurons are inhibited.





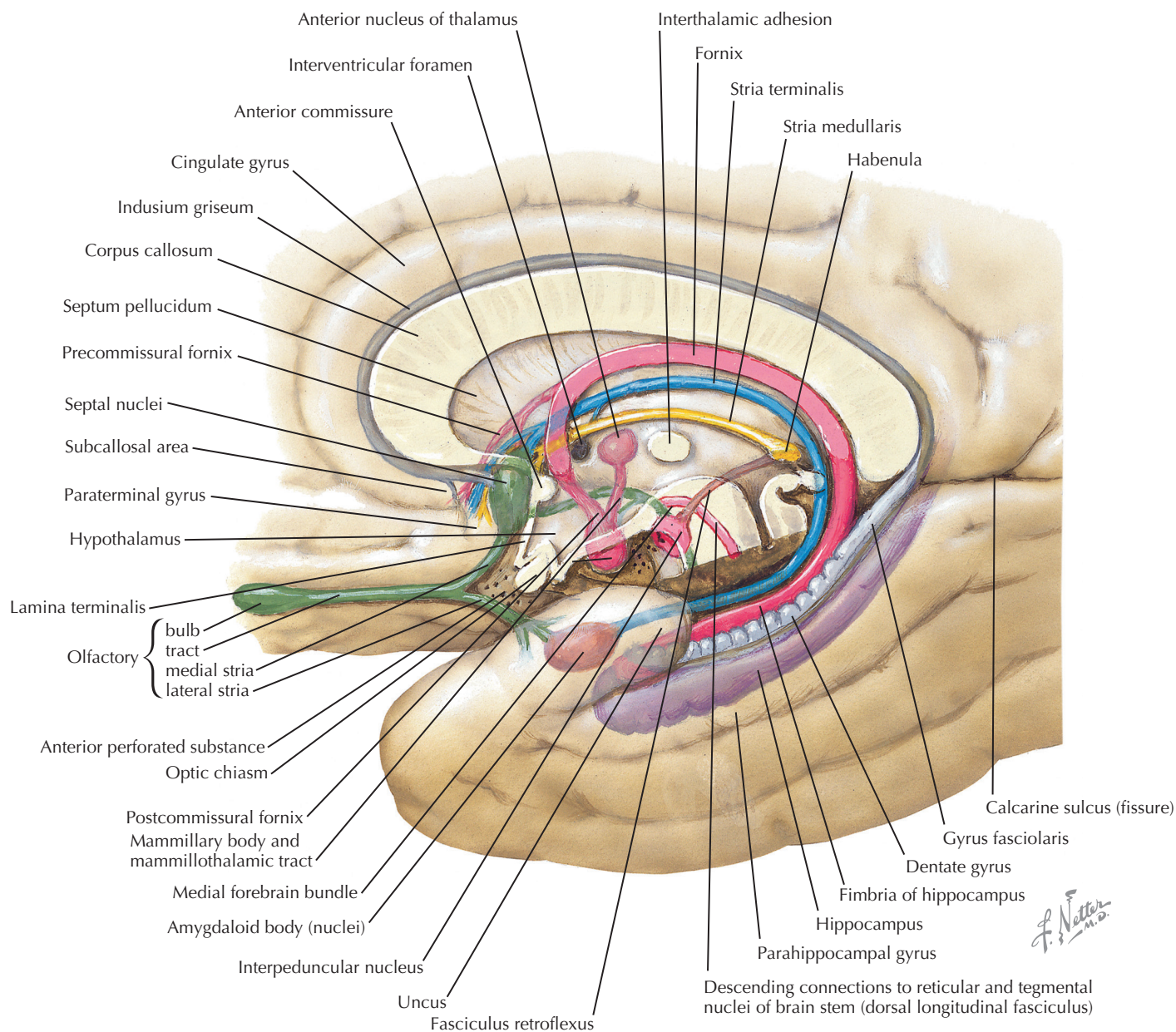
## 16.26 NEUROIMMUNOMODULATION

Connections from the cerebral cortex, limbic forebrain, hypothalamus, and brain stem can exert extensive modulation of autonomic preganglionic outflow and neuroendocrine outflow. Hormones and neurotransmitters from this outflow target lymphoid organs and cells of the immune system. This circuitry provides the substrate for behavior, emotional responsiveness, chronic stressors, and positive complementary and behavioral interventions to influence immune responses. Sympathetic postganglionic noradrenergic fibers directly innervate virtually all organs of the immune system, including (1) primary lymphoid organs (bone marrow, thymus); (2) secondary lymphoid organs (spleen, lymph nodes); (3) mucosa-associated lymphoid organs (gut and lung); and (4) skin-associated lymphoid cells. Vagal postganglionic nerve fibers innervate pulmonary- and gut-associated lymphoid tissue. Pituitary hormones in the circulation (e.g., CRF, ACTH, prolactin, GH, endorphins) and their target organ hormones (cortisol, thyroid hormone) modulate immune reactivity in all lymphoid organs. Cortisol, norepinephrine, and epinephrine are particularly important in mediating chronic stress responses related to immune reactivity. Circulating and local cytokines and inflammatory mediators act on the brain and pituitary to provide feedback information from lymphoid organs (immune-neural signaling), and can modulate CNS neurotransmitter turnover, inflammatory responses, and illness behavior. The gene expression of hormones from secretory cells, cytokines from cells of the immune system, and neurotransmitters from neurons innervating lymphoid organs

can be regulated by the presence of multiple signal molecules in the local environment. Some mediators are produced by neurons, paracrine cells, and cells of the immune system and modulate all of these systems. (GALT, gut-associated lymphoid tissue; MALT, mucosa-associated lymphoid tissue.)

### CLINICAL POINT

The PVN of the hypothalamus is a key regulatory site for neural modulation of immune responses; it acts through both hormonal secretion and autonomic regulation. The principal neural outflow systems that act on peripheral immunocytes are the HPA axis and the SNS connections to organs of the immune system and secretion into the general circulation. Activation of the HPA and the SNS can block some immune defenses, leading to greater susceptibility to viral infections (tenfold in experimental models of murine influenza). Other anterior pituitary hormones also exert immunomodulatory effects. Chronic stressors can influence neural-immune outflow via cortical and limbic connections to the hypothalamus (especially the PVN); chronic stressors exert both HPA and SNS effects that produce diminished cell-mediated immunity and natural killer cell activity. Both immune-inhibiting and immune-enhancing responses can be classically conditioned, a process that requires forebrain involvement and subsequent neural and hormonal outflow (but not cortisol; conditioned immunosuppression occurs in adrenalectomized animals). Both circulating cytokines and endogenous brain cytokines, including IL-1β, IL-6, and TNF-α, can act on the PVN and other CNS sites involved in neuroendocrine and SNS outflow to immune targets, markedly activating cortisol production and catecholamine secretion. In adults, the regulation of secretion of dangerous inflammatory mediators as well as behavioral and lifestyle influences on the HPA axis and SNS may be important components of maintaining robust antiviral and antitumor immunity and may aid in protection from many chronic diseases. These mediators are key components targeted in integrative medical treatment.



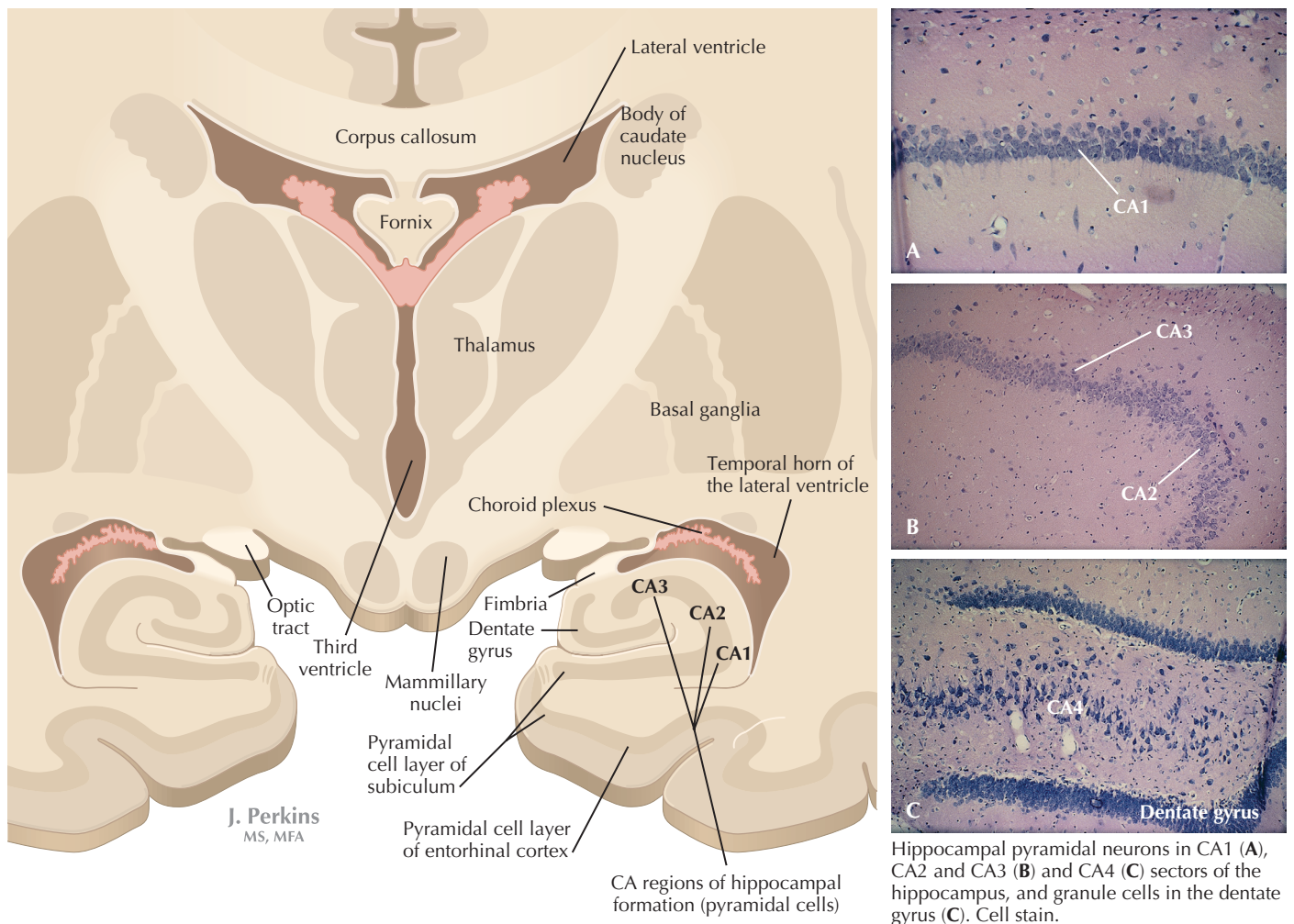
## LIMBIC SYSTEM

### 16.27 ANATOMY OF THE LIMBIC FOREBRAIN

Structures of the limbic forebrain are found in a ring (limbus) that encircles the diencephalon. Two major temporal lobe structures, the hippocampal formation with its fornix and the amygdala with its stria terminalis, send C-shaped axonal projections through the forebrain, around the diencephalon, and into the hypothalamus and septal region. The amygdala also has a more direct pathway (the ventral amygdalofugal pathway) into the hypothalamus. The septal nuclei sit just rostral to the

hypothalamus and send axons to the habenular nuclei via the stria medullaris thalami. The cingulate, prefrontal, orbitofrontal, entorhinal, and periamygdaloid areas of the cortex interconnect with subcortical and hippocampal components of the limbic forebrain and are often considered part of the limbic system. The limbic system is thought to be a major substrate for regulation of emotional responsiveness and behavior, for individualized reactivity to sensory stimuli and internal stimuli, and for integrated memory tasks.





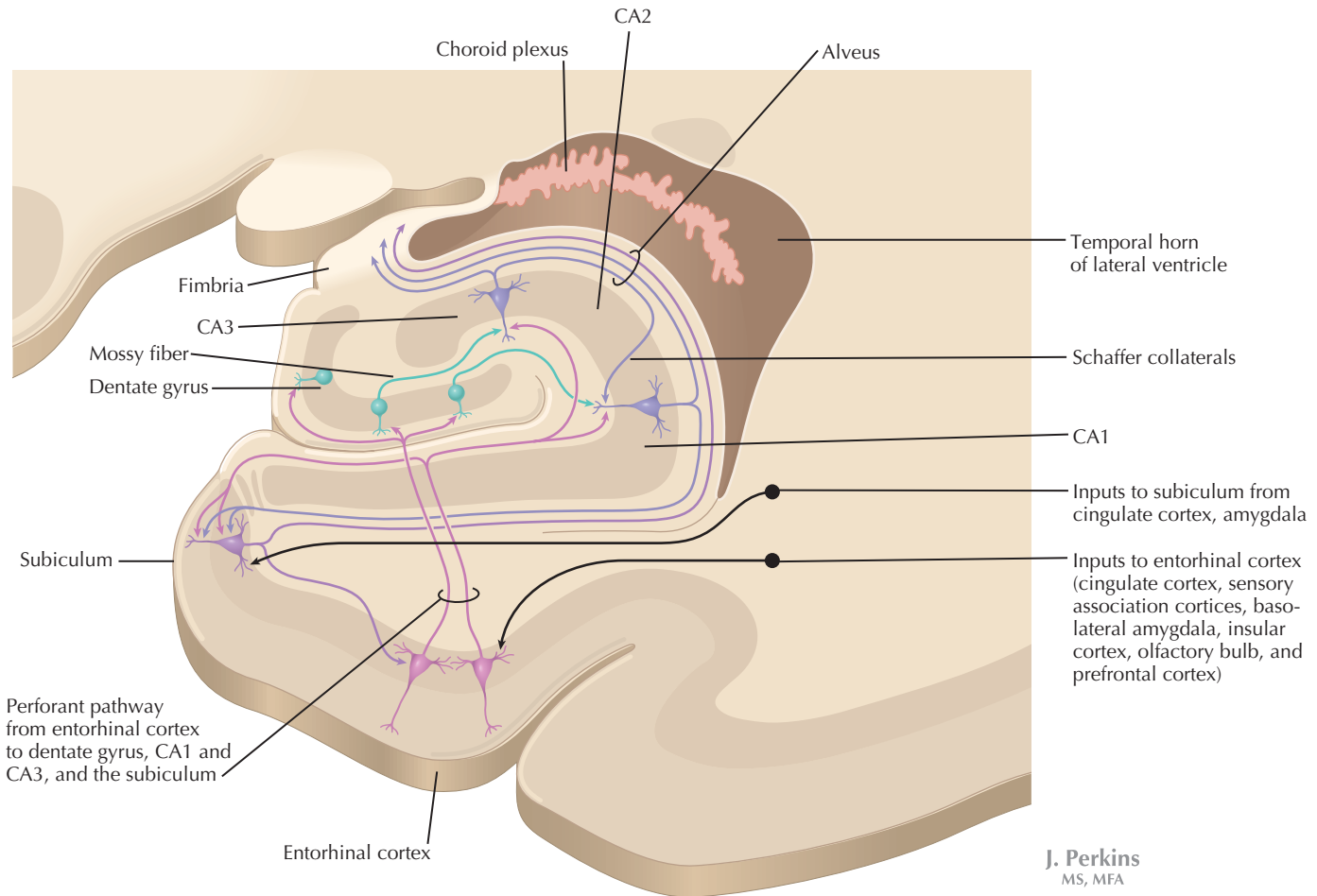
### 16.28 HIPPOCAMPAL FORMATION: GENERAL ANATOMY

The hippocampal formation consists of the dentate gyrus, the hippocampus proper (cornu ammonis [CA] regions), and the subiculum. These structures are intimately interconnected with the adjacent entorhinal cortex. The hippocampus is a seahorse-shaped structure found in the medial portion of the anterior temporal lobe. It bulges laterally into the temporal horn of the lateral ventricle. The hippocampus is divided into several zones of pyramidal cells, called CA regions (CA1–CA4). The dentate gyrus and hippocampus are three-layered cortical regions. Granule cells populate the dentate gyrus, and pyramidal cells are the main neurons in the CA regions of the hippocampus. The hippocampal formation has extensive interconnections with cortical association areas and with limbic forebrain structures, such as the septal nuclei and the cingulate gyrus. The hippocampal formation is involved with consolidation of short-term memory into long-term traces, in conjunction with extensive regions of neocortex.

#### CLINICAL POINT

Pyramidal cells in the CA1 region of the hippocampus are particularly vulnerable to apoptosis resulting from ischemia. Following a heart attack with delayed resuscitation, an episode of cerebral ischemia, or multi-infarct problems, or after increasingly poor blood flow in the anterior circulation to the brain, destruction of CA1 neurons (Sommer's sector) can result in loss of short-term memory and in spatial disorientation. CA3 pyramidal neurons are particularly vulnerable to high or persistently elevated levels of cortisol (or synthetic glucocorticoids), resulting in similar functional deficits. The combination of cerebral ischemia and high cortisol is particularly damaging to the hippocampus. This combination of relative ischemia and high circulating glucocorticoids may occur in older individuals with atherosclerosis and compromised cerebral blood flow (but still free of symptoms) who experience a highly stressful experience (e.g., hospitalization or institutionalization) in which they are exposed to nosocomial organisms and generate cytokine responses, further exacerbating cortisol secretion. This situation may help to precipitate hippocampal damage that leads to consolidation problems relating to immediate and short-term memory and confusion, and produces disorientation, conditions frequently encountered in hospitalized or institutionalized elderly patients.



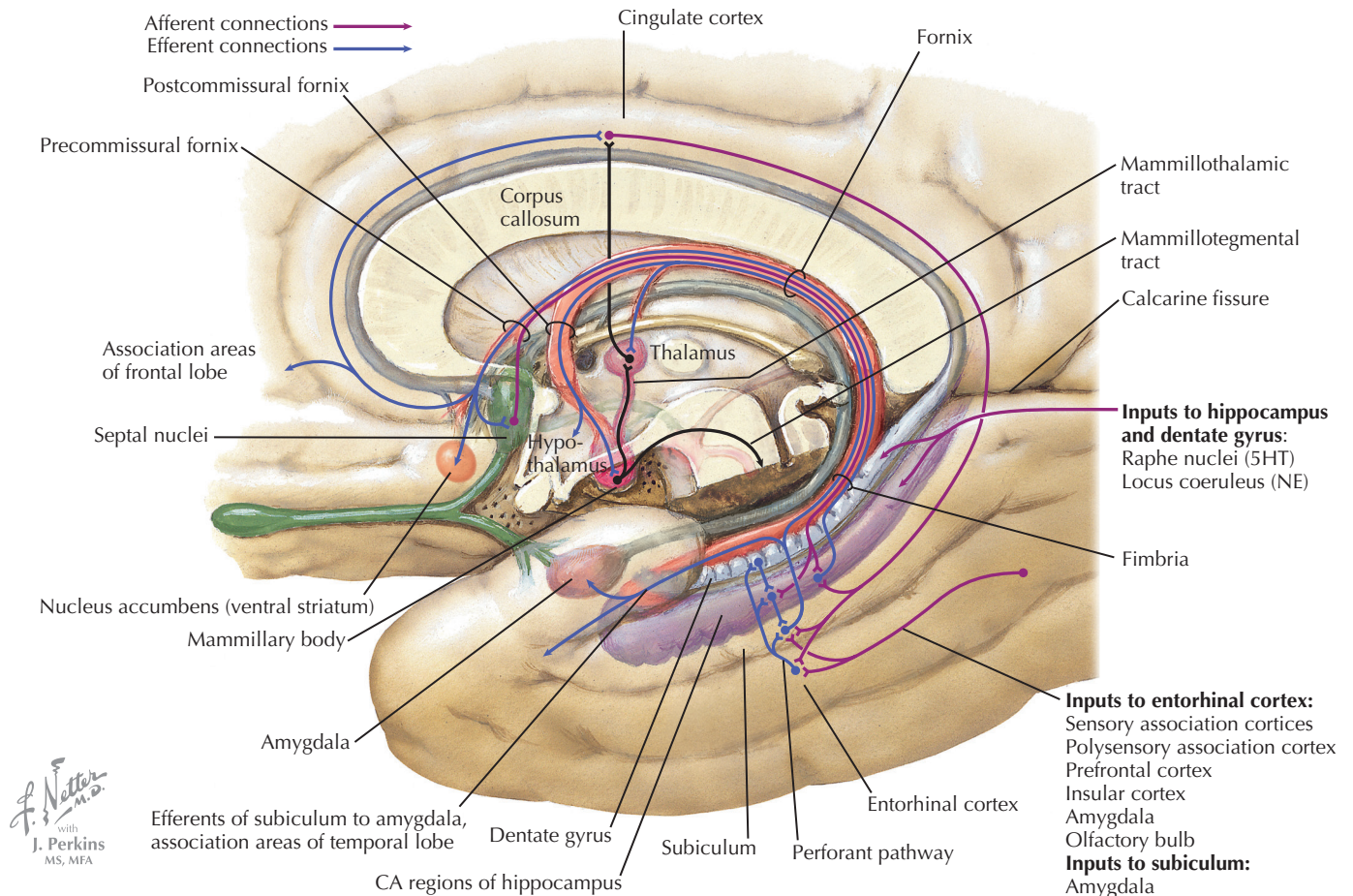


### 16.29 NEURONAL CONNECTIONS IN THE HIPPOCAMPAL FORMATION

The hippocampal formation has an internal circuitry that is interconnected with the entorhinal cortex. Pyramidal neurons of the entorhinal cortex send axons to granule cell dendrites in the dentate gyrus. These granule cell axons (mossy fibers) synapse on pyramidal cell dendrites in CA3. Pyramidal cells in CA3 project to pyramidal cell dendrites in CA1 (Schaffer collaterals) and CA2. CA1 pyramidal axons project to pyramidal neurons in the subiculum. The subiculum sends axonal projections back to the pyramidal neurons of the entorhinal cortex. This information flow represents an internal circuit. Superimposed on this circuitry is a host of interconnections with association regions of the neocortex and other limbic forebrain structures. Neurons of the subiculum and pyramidal neurons of CA1 and CA3 send axons into the fornix as efferent projections to target structures. The subiculum also sends axons to the amygdala and association areas of the temporal lobe.

#### CLINICAL POINT

Many temporal lobe structures are associated with the flow of information through the hippocampal formation, including the hippocampus, subiculum, entorhinal cortex, and associated cortical areas of the temporal lobe. Many of these cortical regions are particularly susceptible to neuronal degeneration in Alzheimer's disease (AD), a neurodegenerative disease that damages and destroys neurons in the cerebral cortex and higher centers of the brain and is accompanied by marked cognitive deficits. Disruption of hippocampal circuitry leads to the inability to consolidate immediate and short-term memory into long-term traces. Temporal lobe damage and disruption of connections with the basal forebrain, cingulate cortex, frontal cortex, and other forebrain structures also affected by AD contribute to the marked cognitive decline in patients with AD. In AD, the brain shows extensive neuronal loss, impaired functioning of synaptic connections, and damage to important neurotransmitter systems that participate in functions such as memory. AD is characterized by the accumulation of altered and aberrant proteins inside neurons, called neurofibrillary tangles, and outside of neurons, called senile plaques. However, severe cognitive decline may occur in the absence of neurofibrillary tangles and senile plaques, and the presence of these proteins in the brain is not always predictive of cognitive dysfunction. Proposed causes of AD include the accumulation of beta-amyloid protein and its precursor protein (in plaques) and/or excessive phosphorylation of an important protein (tau) (in tangles) that helps to give neurons their structural integrity. A form of apolipoprotein E (epsilon 4) is linked with excessive production of free radicals that may kill neurons. Inflammatory molecules (e.g., IL-1beta) also may cause neuronal damage. At present, there is no common agreement on a specific sequence of events or cascade of pathology in AD.



### 16.30 MAJOR AFFERENT AND EFFERENT CONNECTIONS OF THE HIPPOCAMPAL FORMATION

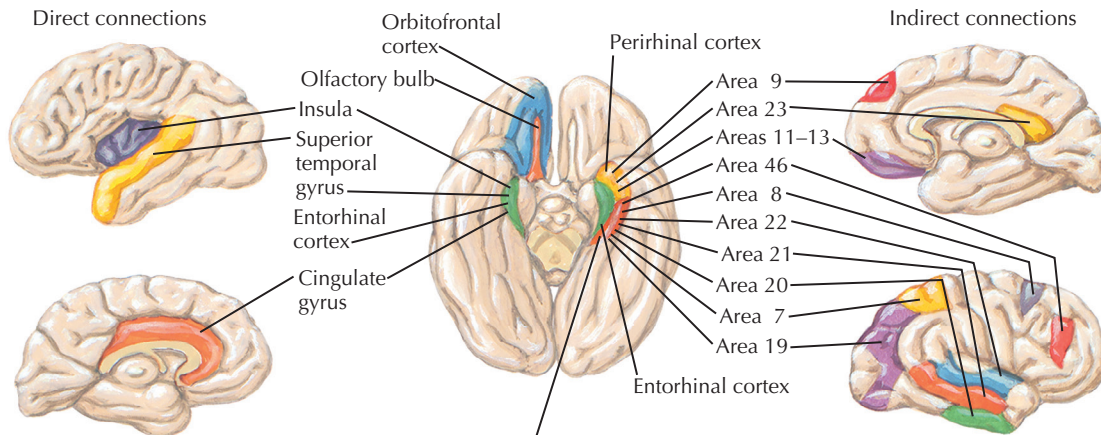
Pyramidal neurons in the subiculum and hippocampal regions CA1 and CA3 give rise to the efferent fornix. The subiculum projects axons to hypothalamic nuclei (especially mammillary nuclei) and thalamic nuclei via the postcommissural fornix. CA1 and CA3 of the hippocampus send axons to the septal nuclei, the nucleus accumbens, the preoptic and anterior hypothalamic regions, the cingulate cortex, and association areas of the frontal lobe. Afferent cholinergic axons from septal nuclei traverse the fornix to supply the dentate gyrus and hippocampal CA regions. Massive inputs arrive in the hippocampal formation from sensory association cortices, polysensory association cortices, the prefrontal cortex, the insular cortex, the amygdaloid nuclei, and the olfactory bulb via projections to the entorhinal cortex. The entorhinal cortex is fully integrated into the internal circuitry of the hippocampal formation. The subiculum is connected reciprocally with the amygdala and also sends axons to cortical association areas of the temporal lobe. (5HT, 5-hydroxytryptamine [serotonin]; NE, norepinephrine.)

#### CLINICAL POINT

Explicit memory is acquisition of information about objects, stimuli, and information that is consciously noted and recallable, and it includes information about personal events, factual knowledge, and information about which cognitive assessment takes place. Explicit memory involves structures in the medial temporal lobe, including the hippocampal formation. Implicit memory is the process of learning how to perform tasks or acquire skills that are not recallable by conscious processes; this form of memory depends upon other brain circuitry and is not lost in classic cases of hippocampal lesions. Explicit memory recall depends upon reassembly of information stored in the brain and involves reconstruction that depends upon sensory perceptions. It is not a video record of the precise external events and can be markedly different from reality, which raises serious questions about the accuracy of “recovered memory” of past events. Explicit memory requires the formation of new synaptic connections and gene expression for new sets of neuronal proteins. The consolidation of immediate and short-term explicit memory into long-term traces involves a process of long-term potentiation, which involves a burst of activity in a specific temporal pattern from an incoming axon; that enhances the likelihood that the target neuron will be activated by this same input and other incoming inputs, providing an increased response to the same magnitude of excitation. Thus, a brief, sustained pattern of input makes it more likely that future synaptic activity will occur. Long-term potentiation occurs in dentate granule cells, CA1 neurons, and CA3 neurons. In the former two neurons, it requires *N*-methyl-*D*-aspartate receptor activation, depolarization,  $\text{Ca}^{++}$  influx, and communication between pre- and post-synaptic elements. In CA3 neurons, long-term potentiation depends on presynaptic  $\text{Ca}^{++}$  influx and subsequent cyclic adenosine monophosphate-dependent protein kinase production.

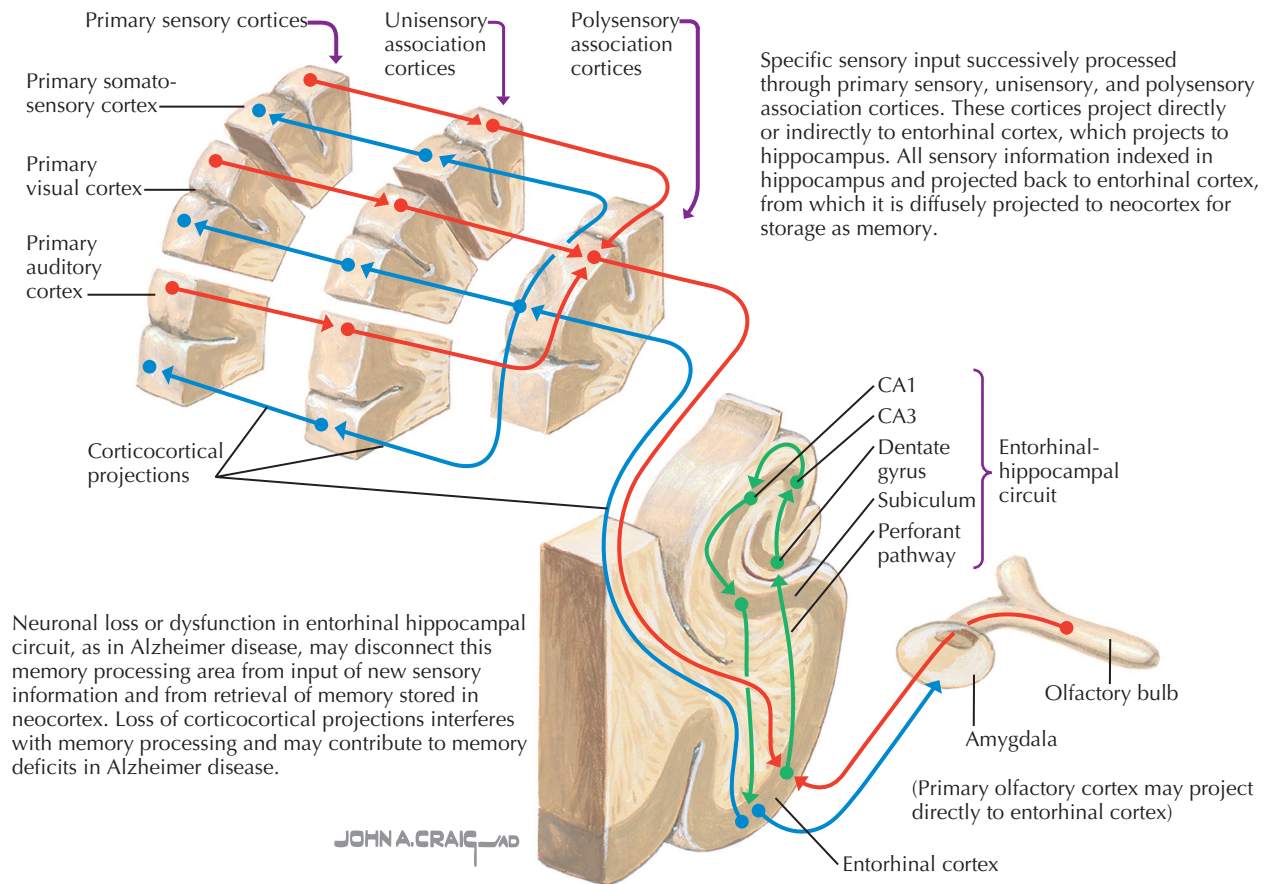


### Afferent and efferent cortical connections of entorhinal cortex



Entorhinal cortex is a major source of projections to hippocampus (major processing center for recent memory). Polysensory association cortices project directly to entorhinal cortex or indirectly via perirhinal cortex or parahippocampal gyrus. Association cortices receive reciprocal projections from entorhinal cortex. Area numbers refer to Brodmann classifications.

### Possible processing circuit for recent memory



### 16.31 AFFERENT AND EFFERENT CONNECTIONS OF THE ENTORHINAL CORTEX

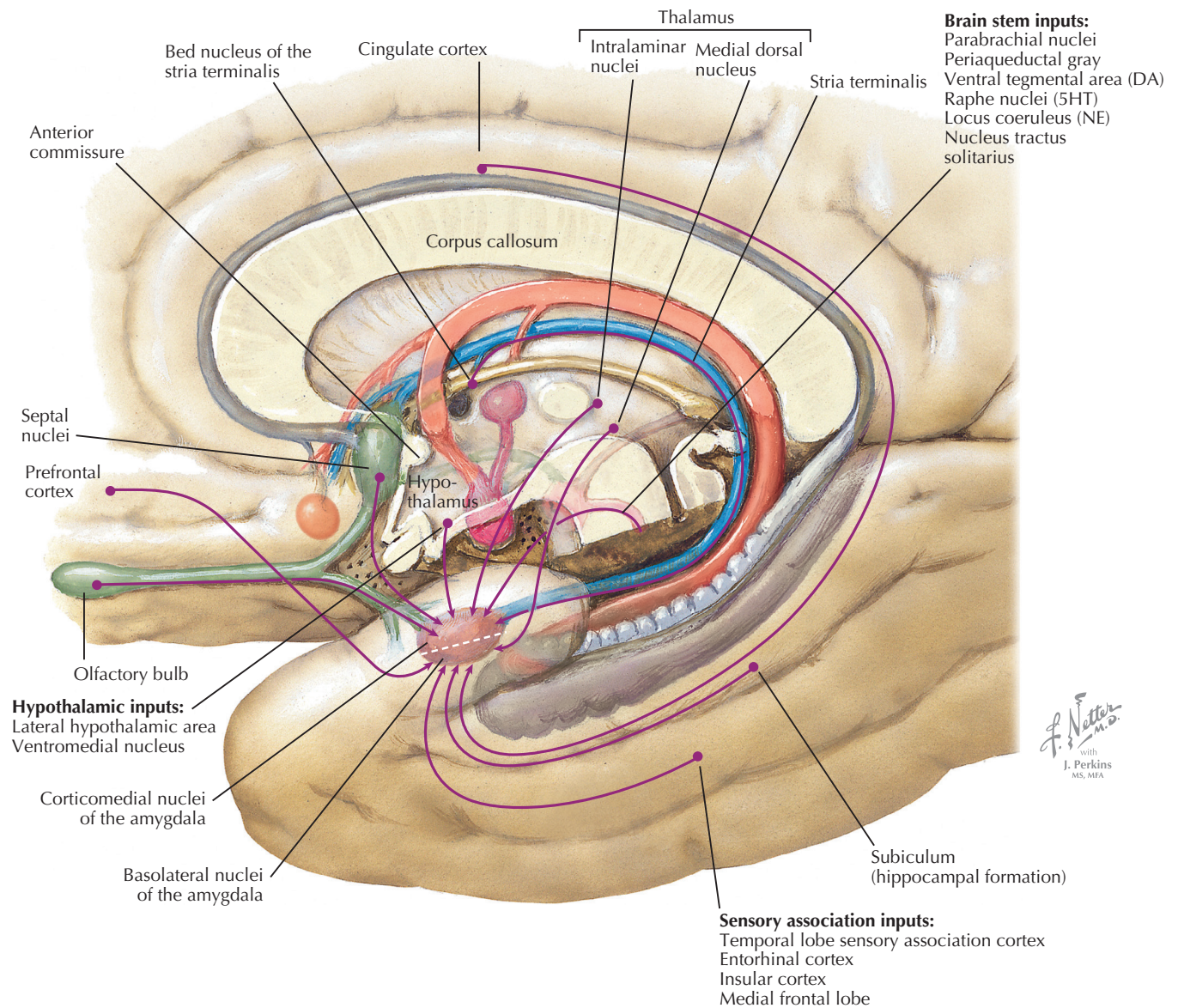
The entorhinal cortex is located in the medial temporal lobe and is integrated into the hippocampal formation circuitry related to memory formation and consolidation and declarative and spatial memory.

Afferents project to the entorhinal cortex from both cortical and subcortical sources. Cortical inputs include association cortex (from all sensory modalities), perirhinal cortex, parahippocampal cortex, orbitofrontal and prefrontal cortex, cingulate cortex, and the hippocampus (to layers V and VI). Subcortical inputs derive from the septal region (especially the cholinergic medial septal nucleus via the fornix), basal fore-

brain (substantia innominate, nucleus of the diagonal band, the olfactory bulb), amygdala (basolateral nuclei), claustrum, thalamus (mainly midline nuclei), and brain stem monoaminergic nuclei (dopaminergic ventral tegmental area, noradrenergic locus coeruleus, and serotonergic rostral raphe nuclei).

Efferent projections are directed to components of hippocampal circuitry, polysensory association cortex, and subcortical regions. For hippocampal circuitry, neurons in layer II project to the dentate gyrus and the CA3 region, and neurons in layer III project to the CA1 region and the subiculum. Efferents to subcortical regions project to the claustrum, nucleus accumbens, and thalamus (medial dorsal nucleus, lateral dorsal nucleus, medial pulvinar).





*F. Netter M.D.*  
 with  
 J. Perkins  
 MS, MFA

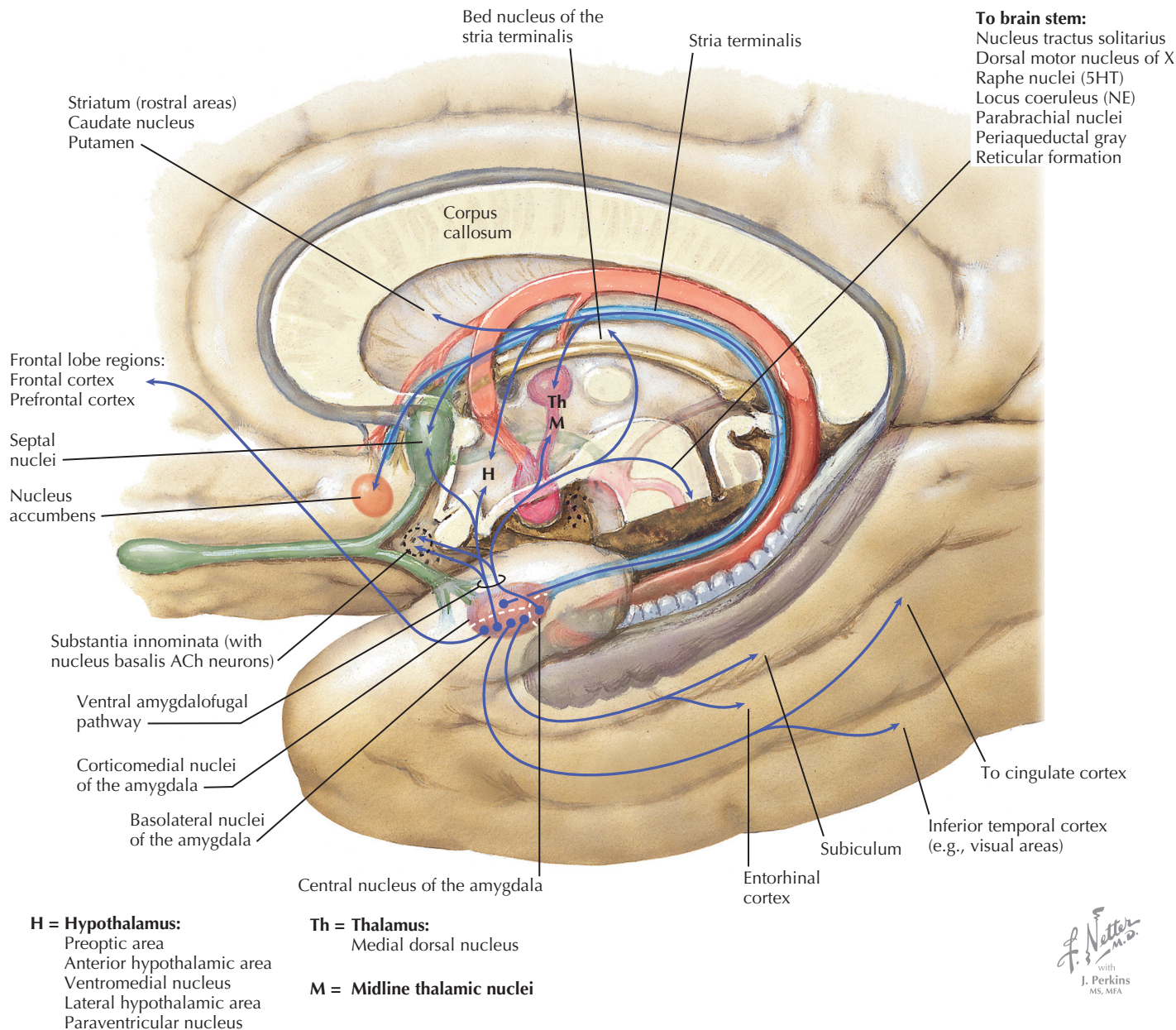
### 16.32 MAJOR AFFERENT CONNECTIONS OF THE AMYGDALA

The amygdala is an almond-shaped collection of nuclei in the medial portion of the anterior temporal lobe. It is involved in the emotional interpretation of external sensory information and internal states. It provides individual-specific behavioral and emotional responses, particularly those involving fear and aversive responses. The amygdala is subdivided into corticomedial nuclei and basolateral nuclei (which receive afferents and project axons to target structures) and the central nucleus, which provides mainly efferent projections to the brain stem. Afferents to the corticomedial nuclei arrive primarily from subcortical limbic sources, including the olfactory bulb, septal nuclei, and hypothalamic nuclei (VM, LHA); the thalamus (intralaminar nuclei); the bed nucleus of the stria terminalis; and extensive numbers of autonomic nuclei and monoamine nuclei of the brain stem. Afferents to the basolateral nuclei arrive mainly from cortical areas, including extensive sensory association cortices, the prefrontal cortex, the cingulate cortex, and the subiculum. (5HT, 5-hydroxytryptamine [serotonin]; NE, norepinephrine.)

#### CLINICAL POINT

The amygdala is a subcortical collection of nuclei in the medial anterior temporal lobe. It is involved in the emotional interpretation and “flavoring” of external sensory information and internal states. Afferents to corticomedial nuclei come from subcortical limbic structures, and afferents to basolateral nuclei derive mainly from cortical structures. Most cases in humans of bilateral destruction of the amygdala occur with trauma or temporal lobe surgery for seizures, and they involve destruction of more than just amygdaloid nuclei. On the basis of primate studies and observations in humans, it appears that amygdaloid lesions result in placid behavior, lack of fear even when confronted with normally fear-provoking stimuli, and withdrawal from social contacts. The normal integration of emotional reactive and cognitive processing is disrupted. Studies have found that patients with bilateral amygdaloid damage cannot recognize facial expressions in others that indicate fear and do not learn or remember events with strong emotional context better than those without such emotional context, as is normally the case. In patients with bilateral temporal lobe damage involving extensive cortical and subcortical neuronal destruction, the Klüver-Bucy syndrome can occur. This syndrome is characterized by placid behavior, loss of fear of potentially dangerous objects, compulsive exploration of the environment (particularly orally), visual agnosias, inappropriately directed hyperphagia (of nonedible items), and hypersexuality. In some cases, loss of consolidation of memory (hippocampal involvement) and cognitive deficits are also seen.



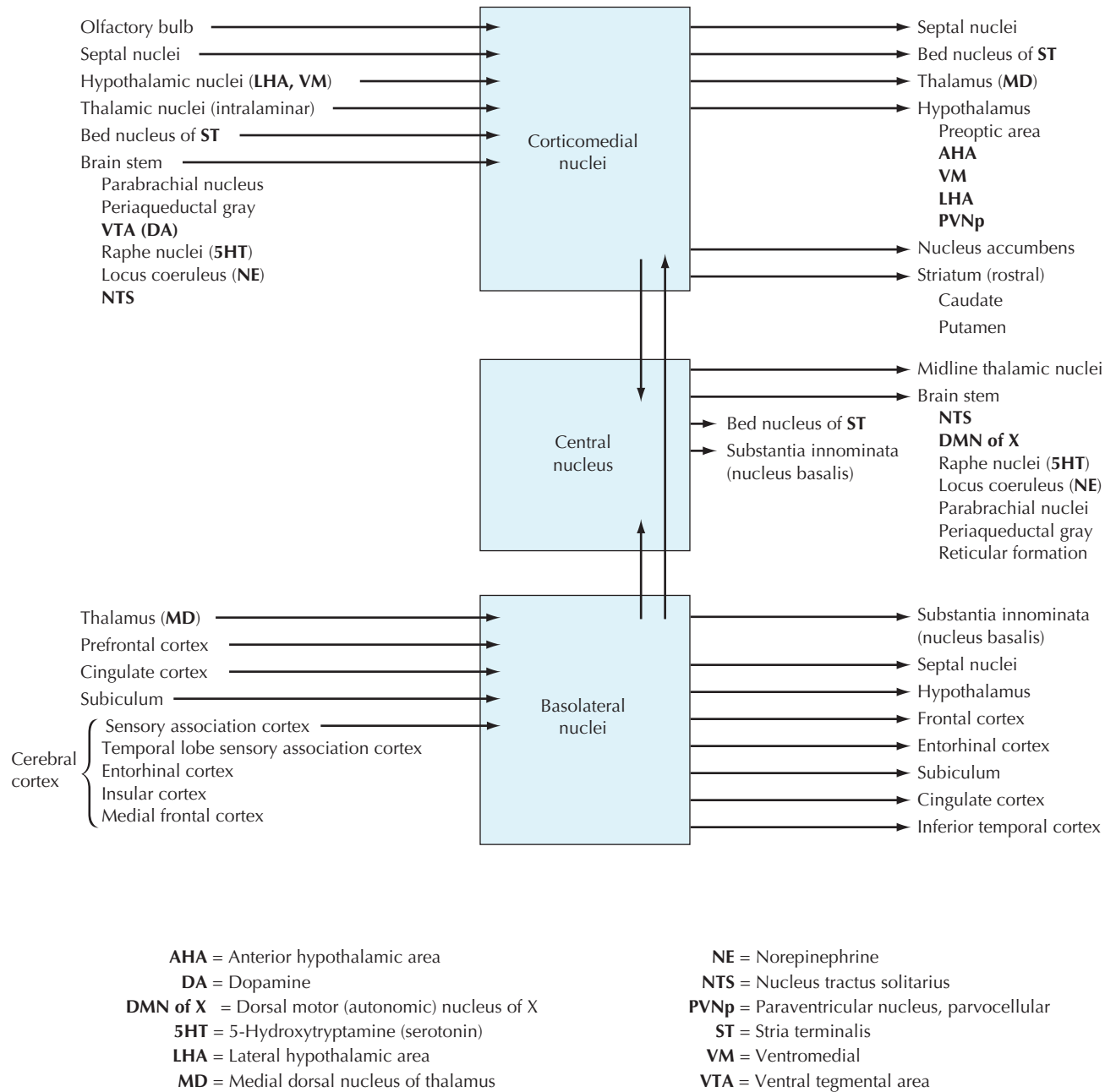


### 16.33 MAJOR EFFERENT CONNECTIONS OF THE AMYGDALA

Efferents from the corticomedial nuclei project through the stria terminalis and are directed mainly toward subcortical nuclei, such as septal nuclei, the mediodorsal (medial dorsal) nucleus of the thalamus, the hypothalamic nuclei, the bed nucleus of the stria terminalis, the nucleus accumbens, and the rostral striatum. Efferents from the basolateral nuclei project through the ventral amygdalofugal pathway to cortical regions, including the frontal cortex, the cingulate cortex, the inferior temporal cortex, the subiculum, and the entorhinal cortex; and to subcortical limbic regions, including hypothalamic nuclei, septal nuclei, and the cholinergic nucleus basalis in substantia innominata. The central amygdaloid receives input mainly from internal amygdaloid connections and sends extensive efferents through the ventral amygdalofugal pathway to autonomic nuclei and monoaminergic nuclei of the brain stem, the midline thalamic nuclei, the bed nucleus of the stria terminalis, and the cholinergic nucleus basalis.

#### CLINICAL POINT

Efferents from the corticomedial nuclei are directed mainly to subcortical limbic nuclei. Efferents from the basolateral nuclei are directed through the ventral amygdalofugal pathway to extensive cortical regions and subcortical structures. The central amygdaloid nucleus sends extensive efferents to brain stem nuclei associated with the machinery of emotional responsiveness provoked by amygdaloid activation. This central nucleus receives its input mainly from other amygdaloid nuclei. Amygdaloid stimulation has been performed in humans (for epilepsy surgery) and in experimental animals. Corticomedial stimulation produces a freezing response (cessation of voluntary movement), automated gestures (lip smacking), and parasympathetic activation that leads to voiding and defecation. Basolateral stimulation produces the vigilance responses of becoming alert and scanning the environment. These responses most likely reflect the outflow of the amygdala to brain stem circuitry that coordinates behavior appropriate to the emotional context of the stimuli. Conditioned fear responses and reactions to stressors require coordinated interaction of neuroendocrine outflow, autonomic reactivity, and behavioral activity. In humans, amygdaloid stimulation results in feelings associated with fear and anxiety. (5HT, 5-hydroxytryptamine [serotonin]; NE, norepinephrine.)



### 16.34 SUMMARY OF MAJOR AFFERENTS, EFFERENTS, AND INTERCONNECTIONS OF THE AMYGDALA

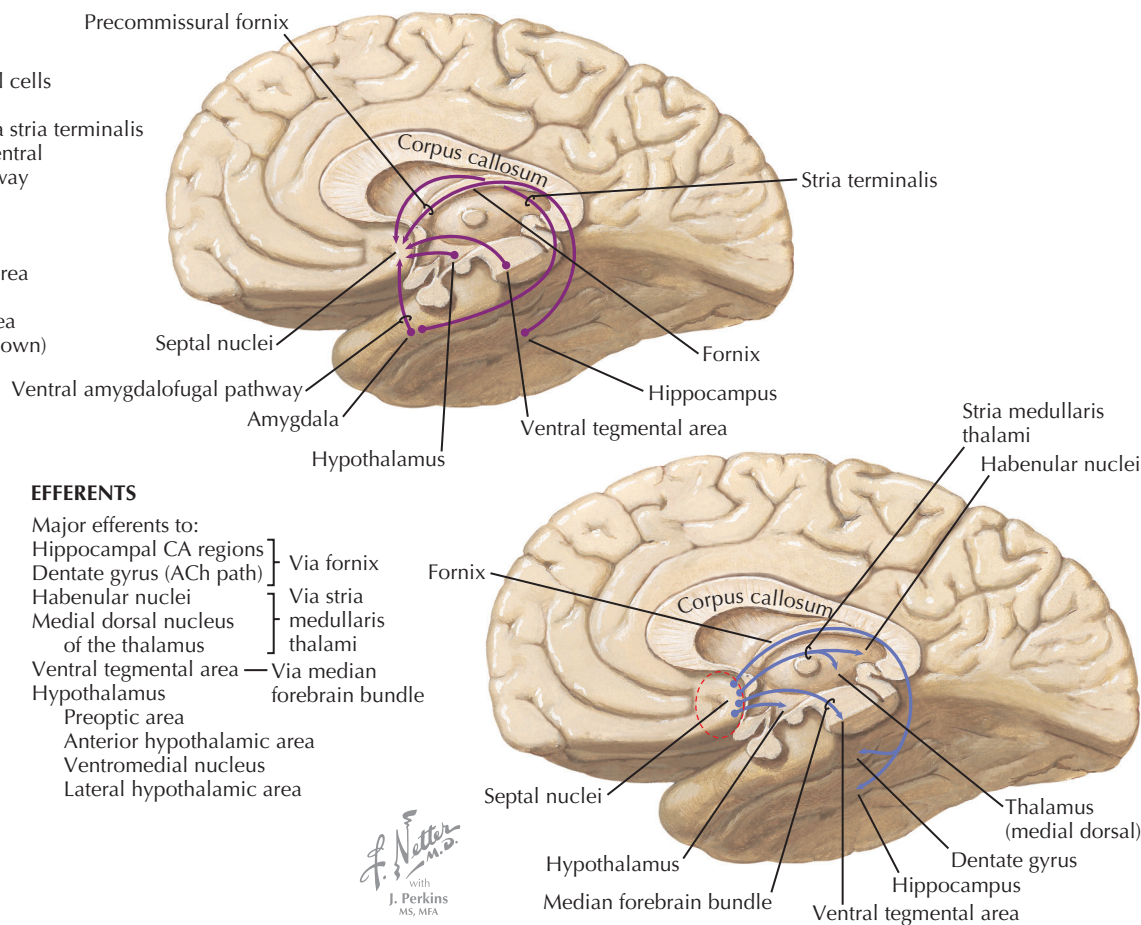
The corticomedial amygdala is connected reciprocally mainly with subcortical limbic forebrain structures and receives extensive additional inputs from brain stem autonomic and monoaminergic nuclei. The basolateral amygdala is connected reciprocally with extensive regions of limbic and association cortex and has additional efferents to subcortical limbic forebrain regions. Both the corticomedial and basolateral nuclei send axons to the central nucleus of the amygdala. The central nucleus has massive descending efferents to extensive auto-

nomic and monoaminergic nuclei of the brain stem as well as to some subcortical limbic forebrain regions. These interconnections with extensive regions of the cortex, the limbic forebrain regions, and the autonomic/limbic brain stem nuclei provide the integrated circuitry that permits analysis of both external and internal information and provides an emotional and interpretive context for the initiation and control of appropriate behavioral and emotional responses. See Figure 15.26 for a brief discussion of the extended amygdala, including the bed nucleus of the stria terminalis and nucleus accumbens.



**AFFERENTS**

Major afferents from:  
 Hippocampal CA pyramidal cells  
 Amygdaloid nuclei  
 Corticomedial nuclei via stria terminalis  
 Basolateral nuclei via ventral amygdalofugal pathway  
 Ventral tegmental area  
 Hypothalamus  
 Preoptic area  
 Anterior hypothalamic area  
 Paraventricular nucleus  
 Lateral hypothalamic area  
 Locus coeruleus (NE; not shown)

**EFFERENTS**

Major efferents to:  
 Hippocampal CA regions } Via fornix  
 Dentate gyrus (ACh path) }  
 Habenular nuclei } Via stria medullaris thalami  
 Medial dorsal nucleus of the thalamus }  
 Ventral tegmental area — Via median forebrain bundle  
 Hypothalamus  
 Preoptic area  
 Anterior hypothalamic area  
 Ventromedial nucleus  
 Lateral hypothalamic area

### 16.35 MAJOR AFFERENT AND EFFERENT CONNECTIONS OF THE SEPTAL NUCLEI

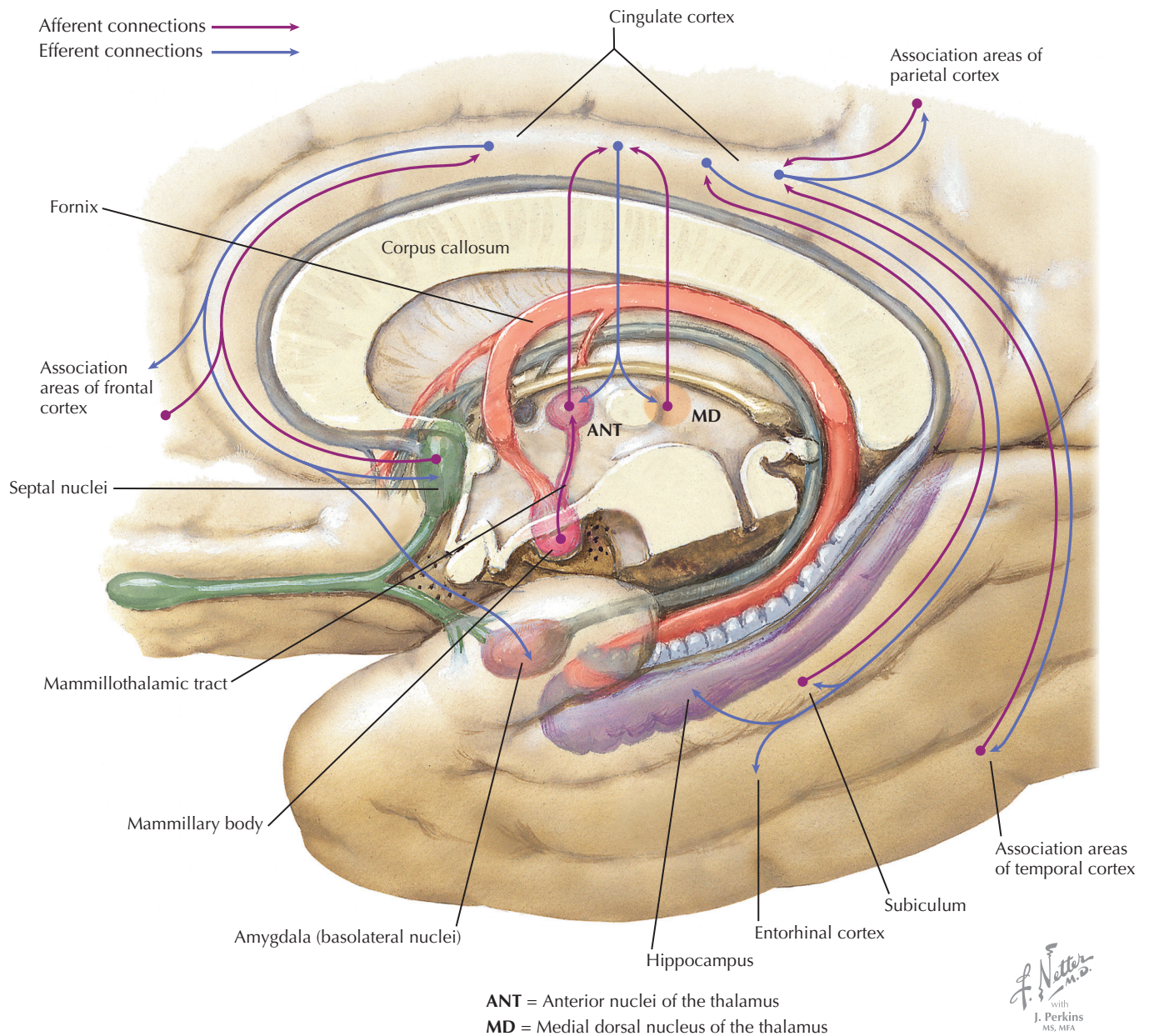
The septal nuclei are subcortical nuclei initially implicated by early ablation and stimulation studies in the regulation of emotional responsiveness such as rage behavior. In experimental studies, the septal nuclei appear to play a role in emotional behaviors, sexual behavior, aggressive behavior, modulation of autonomic functions, and attention and memory functions (from the cholinergic neurons). Afferents to the septal nuclei arrive mainly from the hippocampus, the corticomedial and basolateral amygdala, the ventral tegmental nucleus in the midbrain, and several hypothalamic nuclei. Efferents from the septal nuclei distribute mainly to the hippocampus and dentate gyrus (via the fornix); the habenular nuclei (via the stria medullaris thalami); the medial dorsal nucleus of the thalamus (via the stria medullaris thalami); the ventral tegmental area (via the median forebrain bundle); and several hypothalamic nuclei.

**CLINICAL POINT**

In some humans with ischemic damage involving the septal area, rage behavior has been observed. This is consistent with early experimental

studies in rodents in which septal lesions resulted in exaggerated reactivity to both appropriate and innocuous stimuli (sham rage). In contrast, implanted electrodes in the septal nuclei for electrical self-stimulation studies resulted in prolonged and repeated stimulation, indicative of pleasurable responses.

Efferent connections to the habenula and, via its efferent pathways to the brain stem such as the fasciculus retroflexus (habenulopeduncular tract), and connections to the hypothalamus and brain stem through the descending median forebrain bundle, represent the descending regulatory circuitry from the septal nuclei through which some of the associated behaviors are accomplished. The recent findings that a cholinergic cell group in the septum, along with the bed nucleus of the stria terminalis, sends axons via the fornix to the hippocampal formation, and that these are commonly found to have degenerated in the brains of patients with AD, raises the possibility that these cholinergic neurons are contributors to the process of consolidation of immediate and short-term memory into long-term traces. Damage to the entire collection of cholinergic neurons (including nucleus basalis of Meynert) produces such memory deficits, but experimental studies of selective lesions of cholinergic neurons in the septal nucleus and bed nucleus of the stria terminalis did not result in profound loss of such memory function. It is likely that the cholinergic projections to the hippocampal formation and the cerebral cortex function as a distributive system and affect memory function through an influence on the entire circuitry involved in cognitive and memory functions.



### 16.36 MAJOR CONNECTIONS OF THE CINGULATE CORTEX

The cingulate cortex is located above the corpus callosum. This cortical region is involved in the regulation of autonomic functions (respiratory, digestive, cardiovascular, pupillary); some somatic functions (motor tone, ongoing movements); and emotional responsiveness and behavior. Lesions in the cingulate cortex, like lesions in the orbitofrontal cortex, result in indifference to pain and other sensations that have emotional connotations, and in social indifference. Afferents to the cingulate cortex arrive from association areas of the frontal, parietal, and temporal lobes, the subiculum, the septal nuclei, and the thalamic nuclei (mediodorsal, anterior). Efferents from the cingulate cortex project to association areas of frontal, parietal, and temporal lobes and to limbic forebrain regions, such as the hippocampus, the subiculum, the entorhinal cortex, the amygdala, and septal nuclei. These limbic forebrain regions send extensive projections to the hypothala-

mus for regulation of autonomic and somatic regions of the brain stem and spinal cord.

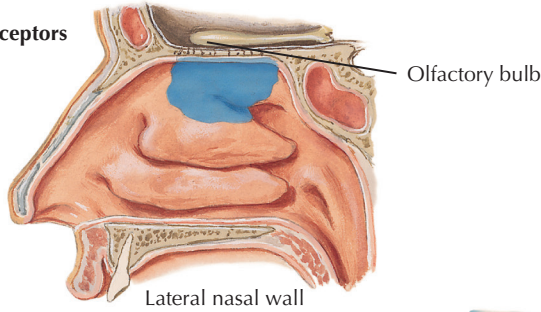
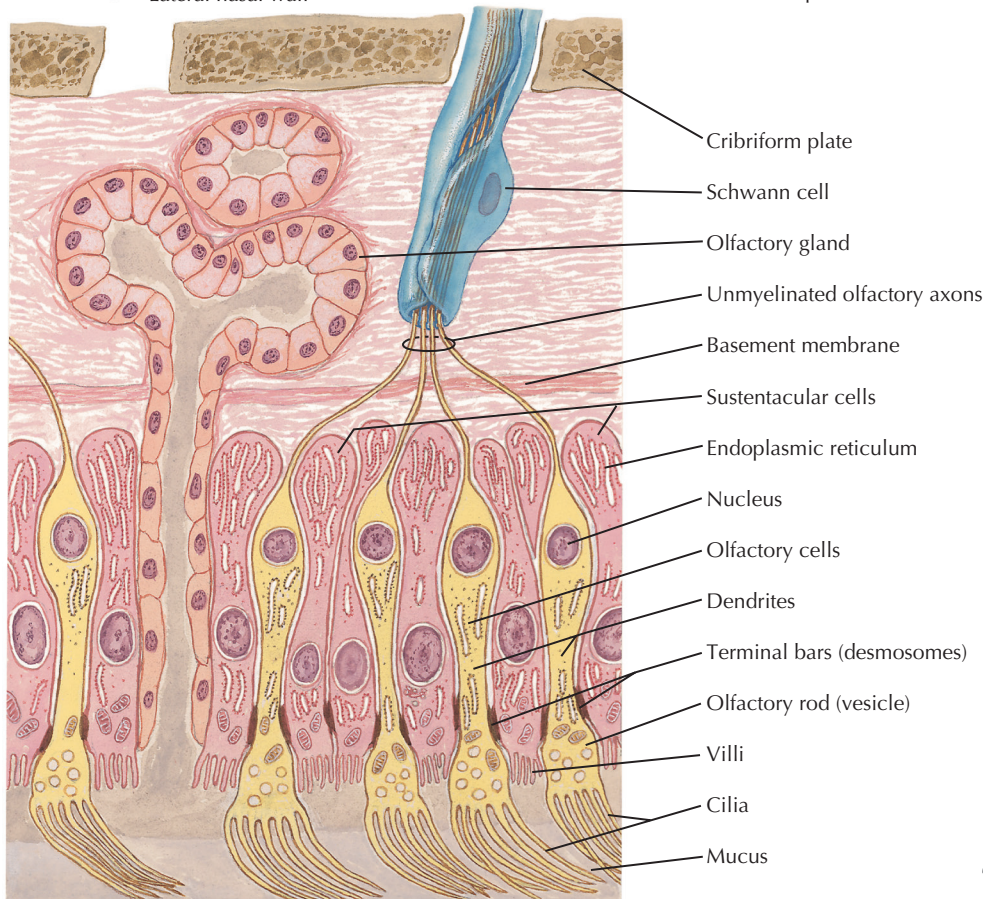
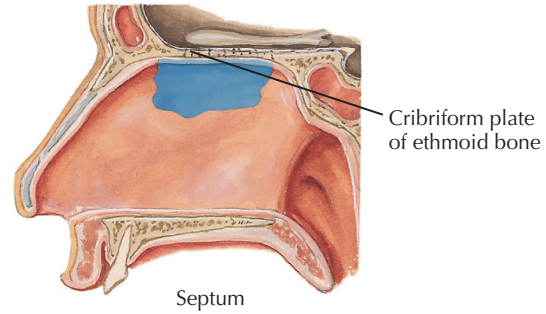
#### CLINICAL POINT

The anterior cingulate cortex may participate in selecting appropriate responses to conflicting stimuli. Inputs to the cingulate cortex derive from many regions of frontal, parietal, and temporal cortex, the subiculum, the septal nuclei, and the medial dorsal thalamus (prefrontal connections). Efferent connections project back to many of these same regions as well as to the amygdala, subiculum, and entorhinal cortex. Through these efferent connections, circuitry to the brain stem can coordinate appropriate autonomic and somatic functions. Lesions in the cingulate cortex result in indifference to pain and other sensations that have strong emotional connotations; they produce social indifference and apathy, eliminate emotional intonation in speech, and cause personality changes. Bilateral anterior cingulate lesions, or cingulotomies, have been done as “psychosurgery” to alleviate intractable pain and to incapacitate anxiety, obsessive-compulsive behavior, and intractable depression. Lesions in the posterior cingulate cortex result in diminished ability to perform spatial navigation.



**A. Distribution of olfactory epithelium** (blue area)

Olfactory Receptors

**B. Schema of section through olfactory mucosa****OLFACTORY SYSTEM****16.37 OLFACTORY RECEPTORS**

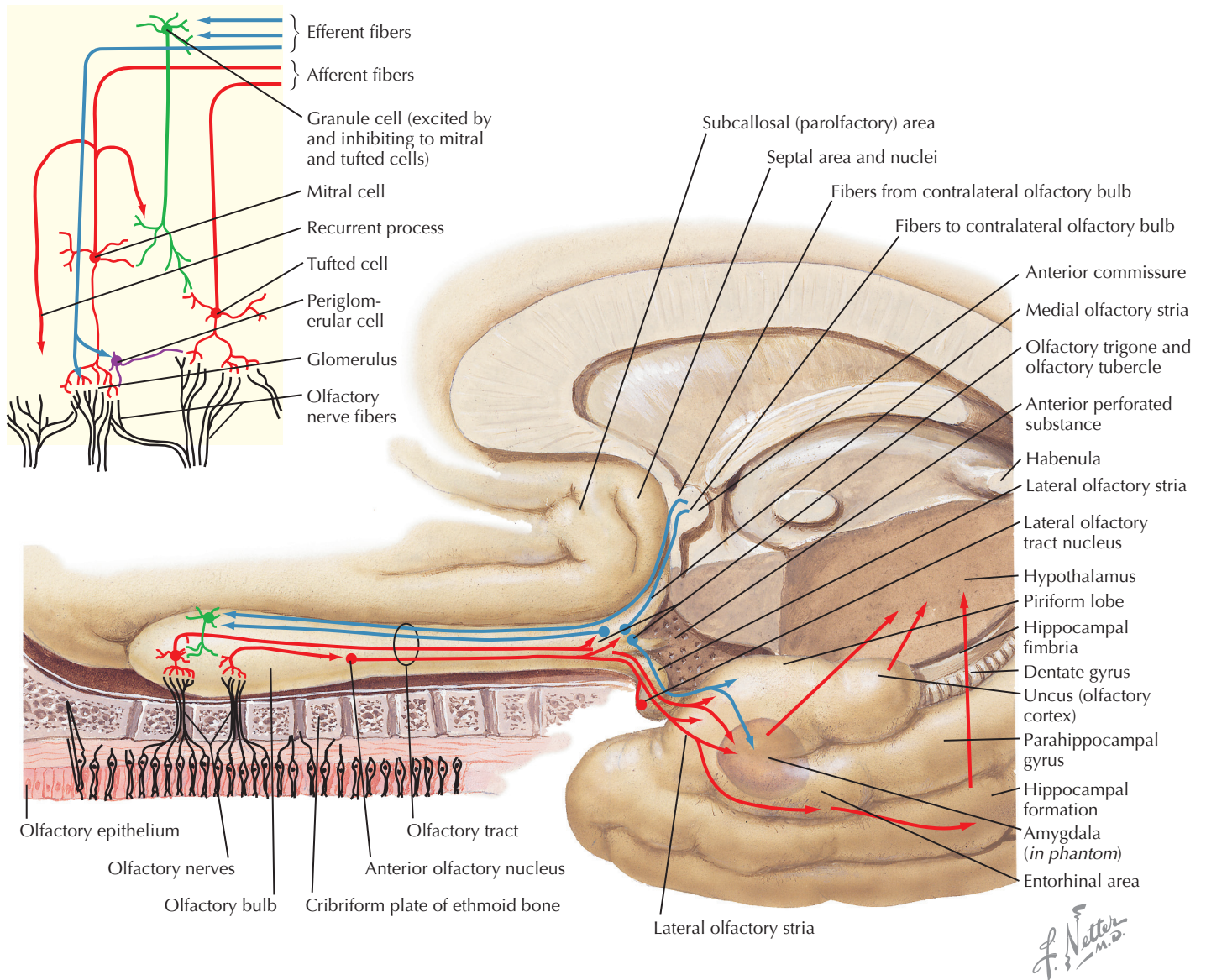
Olfactory receptors are found in a patch of olfactory epithelium that lines the medial and lateral walls of the roof of the nasal cavity. Olfactory receptor cells are primitive, specialized, bipolar neurons whose nuclei are in the base of the epithelium. A dendritic process extends toward the epithelial surface, widening into a rod with 10 to 30 motile cilia that extend into the mucous cover. Odorants act on receptors (G-protein coupled) on these cilia and bring about a slow, depolarizing generator potential. Odorant interactions with receptors are complex, often requiring odorant-binding proteins to carry the odorant through the mucus. The bipolar neurons of the olfactory epithelium are CNS neurons; they are unusual because they undergo continuous replacement and turnover from basal stem cells in the epithelium. The unmyelinated

olfactory axons cluster together in groups (collectively enwrapped by a single Schwann cell sheath) before passing through the cribriform plate. Injuries to the cribriform plate can tear these axons and result in anosmia.

**CLINICAL POINT**

Anosmia, the loss of smell, may not be obvious to a patient; it may present with a blunting of the taste of food. The most common cause of anosmia is a cold, followed by allergic rhinitis. Unilateral anosmia not attributable to local nasal problems suggests involvement of the olfactory nerves, bulb, or tracts and stria. Trauma causing injury to the cribriform plate is the most common cause of olfactory nerve damage. Impairment of olfactory discrimination but with intact ability to detect odors points to possible involvement of forebrain structures, such as limbic circuitry in Wernicke-Korsakoff syndrome, in the prefrontal cortex, in cortical areas damaged by neurodegenerative conditions such as AD, or in thalamic regions.





### 16.38 OLFACTORY PATHWAYS

Primary sensory axons from bipolar neurons pass through the cribriform plate and synapse in the olfactory glomeruli in the glomerular layer of the olfactory bulb. The glomeruli are the functional units for processing specific odor information. The olfactory nerve fibers synapse on the dendrites of the tufted and mitral cells, the secondary sensory neurons that give rise to the olfactory tract projections. Periglomerular cells are interneurons that interconnect the glomeruli. Granule cells modulate the excitability of tufted and mitral cells. Centrifugal connections (from serotonergic raphe nuclei and the noradrenergic locus coeruleus) modulate activity in the glomeruli and periglomerular cells. The olfactory tract bypasses the thalamus and projects to the anterior olfactory nucleus, the nucleus accumbens, the primary olfactory cortex (in the uncus), the amygdala, the periamygdaloid cortex, and the

lateral entorhinal cortex. The olfactory cortex has interconnections with the orbitofrontal cortex, the insular cortex, the hippocampus, and the lateral hypothalamus.

#### CLINICAL POINT

The olfactory bulb and tract can be damaged by meningiomas of the olfactory groove or, less commonly, of the sphenoid ridge. These tumors produce Foster-Kennedy syndrome, which consists of ipsilateral anosmia, ipsilateral optic atrophy resulting from direct pressure, and papilledema caused by increased intracranial pressure. If the ipsilateral optic nerve is completely atrophic, papilledema will not be observed on that side. The olfactory bulb and tract also can be damaged by tumors of the frontal bone, pituitary tumors with frontal extension, frontal tumors such as gliomas that act as mass lesions, aneurysms at the circle of Willis, and meningitis. These conditions are distinguished from the olfactory groove meningiomas by the additional symptoms they cause.

# Index

Page numbers followed by b indicate box (Clinical Point).

## A

- A delta fibers. *see* Small myelinated nerve fibers (A delta fibers)
- A1 nucleus, 282*f*, 347, 347*f*
- A2 nucleus, 282*f*, 347, 347*f*
- A5 nucleus, 282*f*, 347, 347*f*
- A7 nucleus, 347, 347*f*
- A9 nucleus, 349
- A10 nucleus, 349
- Abdominal nerves, and sympathetic ganglia, 214, 214*f*
- Abducens nerve (CN VI), 263*f*
  - and ciliary ganglion, 269, 269*f*
  - clinical point, 268*b*
  - fibers of, in orbit, 267–268
- Abducens nucleus, 394
- Accessory nerve (CN XI), 263*f*, 277, 277*f*
  - clinical point, 277*b*
  - spinal nucleus of, 394*f*
- Acetylcholine, 423*b*
- Acetylcholine (ACh) synapse, 42*f*, 43
- Acoustic schwannoma, 275*b*
- ACTH. *see* Adrenocorticotrophic hormone (ACTH)
- Action potentials, neuronal, 24, 24*f*
  - conduction velocity of, 26, 26*f*
  - in neurotransmitter release, 37, 37*f*
  - propagation of, 25, 25*f*
  - blocking of, 25*b*
- Adamkiewicz, artery of, 113
- Adenohypophysis, 291*f*
- Adequate intrafascicular circulation, pressure gradient necessary for, 158*f*
- Adrenal gland
  - innervation of, 226, 226*f*
  - sympathetic innervation of, 225, 225*f*
- Adrenergic synapses, 201, 201*f*. *see also* Norepinephrine
- Adrenoceptor, alpha and beta, 423*b*
- Adrenocorticotrophic hormone (ACTH), 41, 426, 438*f*, 439, 439*b*
- Affective behavior, diet composition and, 43*b*
- Affective disorders, noradrenergic brain stem pathology in, 347*b*
- Afferent inhibition, of stretch reflex, 244*f*
- Alar plate, 128
  - derivatives of, 141, 141*f*
- Alcohol intoxication, and cerebellar dysfunction, 414*b*
- Alcoholic patients, cerebellar dysfunction in, 74*b*
- Alpha adrenoceptor, 423*b*
- Alpha-gamma coactivation, 245*b*, 246, 246*f*
- Alpha motor neurons, 246*f*, 392, 392*f*
  - classification of axons of, 27*f*–30*f*
- Alternating hemiplegias, 109*b*, 280*b*
- Alzheimer's disease (AD), 350
  - clinical point, 350*b*, 452*b*
  - distribution of pathology in, 351, 351*f*
- Amino acid synapse, 42*f*, 43
- AMPA, 39
- Amygdala, 65*b*, 283*f*
  - clinical point, 455*b*
  - coronal sections through, 322, 322*f*–323*f*
  - development of, 137
  - major afferent connections of, 455, 455*f*
    - summary of, 457, 457*f*
  - major efferent connections of, 456, 456*f*
    - summary of, 457, 457*f*
  - stimulation of, and fear and anxiety, 456*b*
- Amygdaloid body, 64*f*
- Amyotrophic lateral sclerosis, 249*b*, 266*b*
- Analgesic dolorosa, 70*b*
- Anencephaly, 127*b*, 152, 152*f*
- Anhidrosis, 236*b*
- Anions, in neuronal cell membrane, 20
- Anterior cerebral artery (ACA)
  - basal view of, 98
  - frontal view of, 100, 100*b*
  - lateral and medial views of, 105
  - territory of, colored illustration, 106, 106*f*
- Anterior commissure
  - in axial (horizontal) section of forebrain, 304, 304*f*–305*f*
  - in coronal section of forebrain, 320, 320*f*–321*f*
  - in midsagittal section, 55*f*
- Anterior corticospinal tract, 83*f*, 236*f*–239*f*
- Anterior horn cells. *see* Lower motor neurons (LMNs)
- Anterior inferior cerebellar artery (AICA) syndrome, 262*f*
- Anterior (pontine) reticulospinal tract, 83*f*
- Anterior (rostral) perforated substance, 58*f*
- Anterior spinal arteries, 114, 114*f*
  - branches of, supplying medulla, 251*b*
  - cross-sectional view of, 115, 115*f*
  - infarct of, 115*b*
- Anterior (ventral) spinocerebellar tract, 83*f*
- Anterior white commissure, 83*f*, 235*f*–237*f*
- Antidiuretic hormone. *see* Vasopressin
- Antiseizure medications, sites of action of, 33–34, 33*f*
- Aphasia, 346, 346*f*
- Apoptosis, glucocorticoid regulation of, 41, 41*f*
- Appetite, neural control of, 446, 446*f*
- Arachnoid, 49
- Arachnoid granulations, 49, 116*b*
- Arachnoid membrane, 81
- Arcuate fasciculus, 343*f*
- Area postrema, 436, 436*b*, 436*f*
- Arnold-Chiari malformation, 89*b*, 151–152, 151*f*
- Arousal, reticular formation associated with, 284
- Arterial system, 94–115
  - of brain, 95, 95*b*
    - basal view, 98, 98*f*
    - circle of Willis in, 99, 99*f*
    - coronal forebrain section, 101, 101*f*
    - frontal view, 100, 100*f*
    - internal carotid
      - circulation, angiographic anatomy of, 108, 108*f*
      - ophthalmic arteries and, 95, 95*b*, 97, 97*f*
      - lateral and medial views, 105, 105*f*
      - magnetic resonance angiography of, frontal and lateral views, 107, 107*f*
      - meningeal, 94, 94*f*
      - schematic of, 103, 103*f*
      - territories of, color illustration of, 106, 106*f*
    - hypothalamus and pituitary gland, vascular supply to, 112, 112*f*
  - pituitary, 112, 112*f*
  - spinal, 113, 113*f*
    - anterior and posterior, 114, 114*f*
    - vertebrobasilar, 98*b*, 109, 109*b*, 109*f*
    - angiographic anatomy of, 110, 110*f*
    - occlusive sites of, 111, 111*f*
- Ascending pathways, of spinal cord, 83*f*
- Ascending reticular activating system (ARAS), 283*f*
- Ascending sensory fibers, of brain stem and spinal cord, color imaging of, 344*f*
- Aspiny granule cell neuron, 337*f*
- Association fibers, of cerebral cortex, 339*f*
  - bundles, 342, 342*f*
  - clinical point, 341*b*–342*b*
  - neuronal origins of, 340
  - pathways of, 341, 341*f*
- Astrocytes, 7*f*, 8
  - biology of, 9, 9*f*
  - glial process, 4*f*
  - in pia mater, 49
- Atherosclerosis, 96
  - common sites for, 96, 96*f*
- Athetoid movements, 304*b*
- Athetosis, 416*b*
- ATP (adenosine triphosphate), aerobic metabolism of, 4*b*
- Auditory cortex, 53, 53*f*
- Auditory evoked potential, 34, 34*f*
- Auditory nuclei, 283*f*
- Auditory pathways
  - afferent, 373, 373*f*–374*f*
    - clinical point, 374*b*
  - centrifugal (efferent), 375, 375*f*

- Auditory pathways (*Continued*)  
 sound transduction in, 369, 369f  
 clinical point, 369b
- Auditory tecta, 55
- Auerbach's plexuses, 221
- Autonomic-hypothalamic-limbic systems, 421–461  
 autonomic nervous system in, 423  
 hypothalamus and pituitary in, 424–449.  
*see also* Hypothalamus; Pituitary gland  
 limbic system in, 450–459. *see also* Limbic forebrain  
 olfactory system in, 460–461
- Autonomic nervous system (ANS), 198–232, 198f  
 central preganglionic axons of, 129  
 development of, 145, 145f  
 cholinergic and adrenergic synapse, 201  
 development of, 130, 130f, 145, 145f  
 distribution of  
 in abdominal nerves and ganglia, 214, 214f  
 in adrenal gland, 225–226, 225f–226f  
 in cranial nerve fibers, 263  
 in enteric nervous system, 221, 221f  
 in esophagus, 215, 215f  
 in eye, 206, 206f  
 in female reproductive organs, 232, 232f  
 in heart, 213, 213f  
 in immune system and metabolic organs, 199, 199f  
 in kidneys, ureters, and urinary bladder, 228, 228f  
 in limbs, 210, 210f  
 in liver and biliary tract, 223, 223f  
 in male reproductive organs, 231, 231f  
 in nasal cavity, 207, 207f  
 in otic ganglion, 209, 209f  
 in pancreas, 224, 224f  
 in pelvic region, 227, 227b, 227f  
 in pterygopalatine and submandibular ganglia, 208, 208f  
 in small and large intestines, 218, 218f  
 in stomach and duodenum, 217, 217f  
 in tracheobronchial tree, 212, 212f
- neurons of, preganglionic and postganglionic, 423b  
 organization of, 422f, 423  
 postganglionic axons in, 129  
 classification of, 27f–30f  
 myelination of, 18  
 preganglionic neurons of, 7, 198  
 classification of, 27f–30f  
 clinical point, 7b  
 reflex pathways of, 200, 200b, 200f  
 schematic of, 202, 202f
- Autoregulation, of blood flow to brain, 204b
- Axillary nerve, 185
- Axoaxonic synapse, 6f
- Axodendritic synapse, 4, 4f, 6f, 35b
- Axon(s), 4f. *see also* Peripheral nerve(s)  
 alpha motor neuron, classification of, 27f–30f  
 demyelination of, 18b
- Axon(s) (*Continued*)  
 diameter of, myelination and, 27b  
 ensheathment, myelination and, 19  
 gamma motor neuron, classification of, 27f–30f  
 myelinated, 18, 157  
 action potential in, 25  
 conduction of action potential in, 26, 26f  
 peripheral. *see also* Peripheral nerve(s); Peripheral nervous system (PNS)  
 development of, 129, 129f  
 unmyelinated, 157  
 action potential in, 25  
 conduction of action potential in, 26, 26f  
 myelination of, 19
- Axon hillock, 4f
- Axosomatic synapse, 4f, 6f, 35b
- B**
- Basal ganglia, 416–419  
 in axial (horizontal) section, 308, 308f–309f  
 circuitry and neurochemistry in, 417, 417f  
 clinical point, 64b, 304b, 416b  
 connections of, 416, 416f  
 horizontal sections of, 64, 64f  
 motor loop in, 418f  
 nucleus accumbens in, 419, 419f  
 parallel loops in, 418, 418f
- Basal plate, 128  
 derivatives of, 141, 141f
- Basal vein, 121
- Basilar artery, infarct of, 255b
- Basis pontis, motor fibers in, 344f
- Behavioral pathology  
 dopaminergic pathways and, 349b  
 noradrenergic pathways and, 347b  
 and subcortical white matter of forebrain, 341b
- Bell's palsy, 274b
- Benedikt's syndrome, 260b, 262f
- Berry aneurysms, 104b
- Beta adrenergic receptors, 202
- Beta adrenoceptor, 423b
- Beta-endorphin neurons, 364, 364b
- Betz cell, 337f
- Biliary tract  
 autonomic innervation of, 223, 223f  
 clinical point, 223b
- Bipolar cell, 7f
- Bipolar neurons, olfactory, 460
- Blood-brain barrier, 15, 15b, 15f
- Blood pressure regulation, in hypothalamus  
 long-term, 445, 445f  
 short-term, 444, 444f
- Body weight, signaling systems involved in  
 regulation of, 447, 447f
- Bony and membranous labyrinths, 370, 370f
- Botulinum toxin (BOTOX), in  
 neurotransmitter release, 37b
- Boutons, 6f, 18f  
 in synapse, 35f
- Brachial plexus, 181, 181f  
 clinical point, 181b
- Brain, 51–70. *see also* Brain stem; Forebrain; Midbrain  
 arterial supply to, 95, 95f. *see also* Arterial system  
 autoregulation of blood flow to, 204b  
 basal surface anatomy of, with brain stem and cerebellum removed, 58, 58f  
 Brodmann's areas of, 54, 54f, 57f, 59, 59f  
 circumventricular organs of, 436, 436b  
 cisterns of, 86  
 corpus callosum of, 66, 66f. *see also* Corpus callosum  
 cranial nerve primordia of, 143. *see also* Cranial nerves  
 deep venous drainage of, 119, 119f  
 relationship to ventricles, 120, 120f  
 defects of, 152, 152f  
 development of  
 in 2 months, 137f  
 in 3 months, 132f  
 in 5 to 7 weeks, 129f  
 in 6-month and 9-month, 138, 138f  
 in 26–28 days, 129f, 134, 134f  
 in 36-day-old embryo, 135, 135f  
 in 49-day-old embryo and 3-month-old embryo, 136, 136f  
 cranial nerve formation in, 143, 143f  
 eye and orbit formation in, 146, 146f  
 neural proliferation and differentiation in, 132, 132f, 138b, 139  
 pituitary gland, development of, 148, 148f  
 ventricle development in, 149, 149f  
 diet composition and, 43b  
 fornix of, 68, 68f  
 functional regions of, 53, 53b, 53f  
 hemispheres of, midsagittal view of, 55b  
 hippocampal formation in, 68, 68f. *see also* Hippocampal formation  
 imaging of  
 computed tomographic, 60, 60f  
 diffusion-weighted, 67  
 magnetic resonance, 61, 61f. *see also* Magnetic resonance imaging (MRI)  
 positron emission tomographic, 63, 63f  
 lateral view of, 53, 53f–54f  
 limbic structures of, 65, 65f. *see also* Limbic forebrain  
 medial (midsagittal) surface anatomy of, 55, 55f  
 with brain stem removed, 56, 56f  
 functional, 57, 57f  
 meninges of, 49, 49f. *see also* Meninges  
 sex steroid hormones in, 426  
 surface anatomy of, 52, 52f  
 thalamus of, 69, 69f–70f. *see also* Thalamus  
 topographic organization of, 53b
- Brain derived neurotrophic factor (BDNF), 12f
- Brain primordia, adult derivatives of, 142f
- Brain stem, 71–75, 247–287  
 afferent fibers to, 283f  
 alar and basal plate derivatives in, 141, 141f  
 anterior anatomy of, 73, 73f



- Brain stem (*Continued*)  
 arteries of, 111, 111f  
 at 6 months, 138  
 cerebellum and, 285–287, 285f. *see also* Cerebellum  
 clinical point  
   affective disorders and depression, 347b  
   bulbar palsy and pseudobulbar palsy, 249b  
   lateral medullary syndrome, 251b  
   lateral pontine syndrome, 256b  
   medial inferior pontine syndrome, 253b  
   mid-brain displacement and changes in brain function, 258b  
   pontine hemorrhage, 255b  
   unipolar depression, 348b  
   Weber's syndrome, Benedikt's syndrome, 260b  
 cranial nerves, schematic distribution of sensory, motor, and autonomic fibers, 263. *see also* Cranial nerves  
 cross-sectional anatomy of, 248  
   at genu of facial nerve, 255f  
   at level of CN IV and locus coeruleus, 257f  
   at level of CN X and vestibular nuclei, 252f  
   at level of cochlear nuclei, 253f  
   at level of decussation of pyramids, 248f  
   at level of dorsal column nuclei, 249f  
   at level of facial nucleus, 254f  
   at level of inferior colliculus, 258f  
   at level of inferior olive, 251f  
   at level of medial geniculate body, 260f  
   at level of midbrain, 258f  
   at level of midbrain-diencephalon junction, 261f  
   at level of obex, 250f  
   at level of pons, 248f  
   at level of posterior commissure, 261f  
   at level of superior colliculus, 259f  
   at level of trigeminal motor and main sensory nuclei, 256f  
   at medullo-pontine junction, 253f  
 efferent connections to nuclei in, 283f  
 lower motor neuron distribution in, 394, 394f  
 motor and preganglionic autonomic nuclei development in, 145, 145f  
 noradrenergic pathways of, 347, 347f  
   clinical point, 347b  
 posterolateral anatomy of, 72, 72f  
 reticular formation of, 281–284  
   nuclei of, in brain stem and diencephalon, 282  
   pattern of nuclei in brain stem, 281  
 retinal projections to, 386, 386f  
 serotonergic pathways from, 348, 348f  
   clinical point, 348b  
 tegmental cholinergic group in, 350f  
 venous drainage of, and cerebellum, 123, 123f
- Brain stem arterial syndromes, 262  
 Brainstem auditory evoked potentials, 34, 34f  
 Branchiomotor neurons, 145  
 Broca aphasia, 346f  
 Broca's area, 53f  
   functional magnetic resonance imaging of, 345f  
 Brodmann's areas, of brain, 54, 54f  
   on basal surface, 59, 59f  
   on medial surface, 57f  
 Brown-Séquard lesion, 236b  
 Bulbar polio, 249b, 266b
- C**  
 C fibers. *see* Primary somatosensory unmyelinated afferents (C fibers)  
 Calcarine cortex, in midsagittal section, 55f  
 Calcarine fissure, 57f  
 Calcarine sulcus, 55f–56f, 58f  
*Campylobacter jejuni* enteritis, 82b  
 Cardiac function, hypothalamic regulation of, 443, 443f  
 Cardiac muscle, neuroeffector junctions of, 173  
 Cardiovascular autonomic neuropathies, 213  
 Carotid body, 168  
 Carotid endarterectomy, 95b  
 Carotid sinus, 168  
 Carotid venograms, 121, 121f  
 Carpal tunnel syndrome, 189, 189f  
 Catecholamine, 226. *see also* Dopaminergic pathways; Noradrenergic pathways; Norepinephrine  
 Catecholamine synapse, 42f, 43  
 Catecholaminergic neurons, 281  
 Cations, in neuronal cell membrane, 20  
 Cauda equina, 80, 80b, 82, 241, 241f  
 Caudate nucleus, 64, 416, 416f  
   development of, 137  
   head of  
     in axial (horizontal) section, 306, 306f–307f, 310, 310f–311f  
     coronal section through, 318, 318f–319f  
   as radiologic landmark, 86  
 Cavernous sinus, 95  
 Cell body, 4, 4f  
 Cell of Martinotti, 337f  
 Central cholinergic pathways, in nucleus basalis (of Meynert) and in septal nuclei, 350, 350f  
   clinical point, 350b  
 Central nervous system (CNS). *see also* Brain; Brain stem; Spinal cord  
   axonal transport in, 17, 17f  
   axons in, myelination by oligodendroglia, 18, 18f  
   development of  
     in 5 to 7 weeks, 129f  
     6-month and 9-month, 138, 138f  
     in 26–28 days, 129f  
     in 49-day-old embryo and 3-month-old embryo, 136f  
   brain and skull defects in, 152, 152f  
   comparison at 5.5 weeks and adult, 140, 140f
- Central nervous system (CNS) (*Continued*)  
   cranial nerve formation in, 143, 143f  
   development of ventricles in, 149  
   eye and orbit formation in, 146, 146f  
   neural proliferation and differentiation in, 132, 132f, 138b, 139  
   pituitary gland, development of, 148, 148f  
   ventricle development in, 149f  
 inflammation in, 16, 16f  
 neural tube defects in, 151, 151f  
 neurons of, 7  
   myelination of axons of, 134b  
   nociceptive modulation in, 364, 364b  
   origin of, 133, 133f  
   stem cells in, intrinsic and extrinsic mechanisms of, 13, 13f  
 Central preganglionic axons, development of, 145, 145f  
 Central (rolandic) sulcus, 53f, 55f  
 Centrum semiovale, 314, 314f–315f  
 Cerebellar glomerulus, 6f  
 Cerebellar peduncles, 72, 75, 287, 287f  
   clinical point, 72b, 287b  
   and fourth ventricular anatomy, 88  
   superior and middle, 344f  
 Cerebellopontine angle, 275b  
 Cerebellovestibular pathways, 414, 414f  
   clinical point, 414b  
 Cerebellum, 57f, 71–75, 142, 247–287, 409–415  
   afferent connections in, 411, 411f  
   afferent pathways to, 412, 412f  
     clinical point, 412b  
   alcohol and dysfunction of, 74b  
   alcohol intoxication and dysfunction of, 414b  
   anatomical organization of, 285  
     deep nuclei and cerebellar peduncles, 287  
     lobes and regions, 285, 285f  
     lobules, 286, 286f  
   anatomy of  
     external, 74, 74f  
     internal, 75, 75f  
   cerebellovestibular and vestibulocerebellar pathways in, 414, 414f  
   clinical point, 285b–287b  
     drug toxicity in, 410b  
   complex arrays of synapses in, 6b  
   deep nuclei of, 283f, 411, 411f  
   development of, 136  
   efferent connections in, 283f, 287f  
   efferent pathways in, 413, 413f  
     clinical point, 413b  
     to upper motor neuron systems, 415, 415f  
   functional subdivisions of, 409, 409f  
   lateral view of, 286f  
   medial view of, 55f  
   motor channels, 164  
   neuronal circuitry of, 410, 410f  
   posterior view of, 286f  
   venous drainage of, 123, 123f  
 Cerebral aneurysms, common site of, 104  
 Cerebral aqueduct, 55f, 58f, 89

- Cerebral arteries. *see also* Anterior cerebral artery (ACA); Middle cerebral artery (MCA); Posterior cerebral artery (PCA)  
territory of, colored illustration, 106
- Cerebral cortex, 52, 138  
afferents to, 283f  
areas of damage, 346, 346f  
association fibers of, 339f  
bundles, 342, 342f  
clinical point, 341b–342b  
color imaging of, sagittal and axial views, 343, 343f  
neuronal origins of, 340  
pathways of, 341, 341f  
Brodman's areas of, 54  
corticobulbar tract, 397f  
corticospinal tract, 398f  
efferent connections in, 283f, 339, 339f  
clinical point, 339b  
neuronal origins of, 340, 340f  
efferent pathways of, 395f  
color imaging of, 396, 396f  
functional characteristics of, 52b  
functional regions of, 53  
functional magnetic resonance imaging of, 345f  
layers of, 336, 336f  
neuronal cell types in, 337, 337f  
processing of nociceptive information and, 359–361  
projection fibers of, 339f  
color imaging of, 343–344, 343f–344f  
neuronal origins of, 340  
underlying, 58  
vertical columns of, 338, 338f
- Cerebral longitudinal fissure, 58f
- Cerebral peduncles, 58f, 142
- Cerebral veins, 116b, 122, 122f
- Cerebrospinal fluid (CSF), 85–91  
analysis of, by spinal tap, 80b  
circulation of, 91, 91f  
blockage of flow of, 86  
from fourth ventricle, 89, 89b  
from lateral ventricles to third ventricle, 87  
obstruction of, 149b  
composition of, 86f
- Cerebrovascular occlusive disease, common sites of, 96, 96f
- Cerebrovascular “strokes”, 105b
- Cervical dermatomes, 131
- Cervical disc herniation, 183, 183f
- Cervical muscles, and diaphragm, 178
- Cervical plexus, 178, 178f  
clinical point, 178b  
fibers of, motor, sensory and proprioceptive, 178  
in head and neck, 176, 176f  
schema, 177, 177f, 191f  
in situ, 177, 177f
- Cervical spinal cord  
at gray matter organization, 235  
magnetic resonance images of, 241
- Cervical vertebrae, arteries surrounding spinal cord and, 113f
- Chandelier cell neuron, 337f
- Chemical neurotransmission, 42f, 43
- Cholinergic muscarinic receptor (M1–M3), 423b
- Cholinergic synapses, 43, 201, 201f. *see also* Acetylcholine  
in tracheobronchial tree, 212
- Chorea, 416b
- Choreiform movements, 304b, 308b
- Choroid plexus, 55f, 86–87, 89b
- Chromaffin cells, medullary, 225
- Ciliary ganglion, 203, 422f  
and extraocular nerves, 269, 269f
- Ciliary neurotrophic factor (CNTF), 12f
- Cingulate cortex, 459, 459f  
clinical point, 459b
- Cingulate gyrus, 55f–56f, 58f
- Cingulate sulcus, 55f
- Cingulum, 342f, 344f
- Circadian rhythms, hypothalamic regulation of, 425
- Circle of Willis, 98  
and cerebral aneurysms, 104  
schematic illustration and vessels in situ, 104, 104f
- Circumventricular organ, 425, 436, 436f  
clinical point, 436b
- Cisterns, magnetic resonance imaging of, 62
- Climbing fibers, 410–411, 410f–411f
- Coccygeal plexus, 192, 192f
- Coccyx, 78f
- Cochlear nerve, 374
- Cochlear nuclei, 253f, 283f
- Cochlear receptors, 372, 372f
- Collateral ganglia, 423  
sympathetic, 198
- Collateral sulcus, 56f, 58f
- Combined synapse, 6f
- Commissural fibers, 66  
of cerebral cortex, 339f  
neuronal origins of, 340
- Common carotid artery, bifurcation of, 95, 95b
- Complex regional pain syndrome (CRPS), 363–364, 363b
- Compression neuropathy, 159  
electrodiagnostic studies in, 28f
- Computed tomography scans, coronal and sagittal, 60, 60f
- Conduction velocity evaluation, 196b
- Conduction velocity studies, 28
- Contralateral hemiplegia, 99b
- Conus medullaris syndrome, 241b
- Cornu ammonis, 68
- Corona radiata, and internal capsule, 344f
- Corpus callosum, 55f, 343f  
anatomy of, 66, 66f  
in axial (horizontal) sections, 312, 312f–313f  
clinical point, 322b  
color imaging of, 67, 67f  
fibers in, 344f  
in coronal section, 316, 316f–317f  
development of, 137  
genu of, 58f  
in axial (horizontal) section, 310, 310f–311f
- Cortical association bundles, 342, 342f. *see also* Association fibers, of cerebral cortex
- Cortical neurons, 139  
electrical firing patterns of, 31, 31f
- Cortical projection fibers, 343f
- Corticoautonomic fibers, 339f
- Corticobulbar tract (CBT), 339f, 397, 397f  
clinical point, 399b
- Corticobulbospinal system, 339f
- Corticohypothalamic fibers, 339f
- Cortic limbic fibers, 339f
- Corticonigral fibers, 339f
- Corticonuclear fibers, 339f
- Cortico-olivary fibers, 339f
- Corticopontine fibers, 339f
- Corticoreticular afferents, 283f
- Corticoreticular pathways, 404, 404f
- Corticoreticulospinal system, 339f
- Corticorubrospinal system, 339f
- Corticospinal tract (CST), 83, 398f, 399  
clinical point, 399b  
terminations of, in spinal cord, 400, 400f, 406
- Corticostriatal connections, 418
- Corticostriate fibers, 339f
- Corticosubthalamic fibers, 339f
- Corticotectal fibers, 339f
- Corticothalamic projections, 339f
- Corticotropin releasing hormone (CRH), 41, 112b
- Cortisol, 449, 449f
- Cranial colliculus. *see* Superior colliculus
- Cranial fossa, 46f
- Cranial nerves, 263. *see also specific nerve*  
I (olfactory), 263f  
II (optic), 263f, 267  
III (oculomotor), 263f, 267, 269, 269f  
IV (trochlear), 263f, 267, 269, 269f  
V (trigeminal), 263f, 270f, 271  
VI (abducens), 263f, 267, 269, 269f  
VII (facial), 263f, 267, 273, 273f  
VIII (vestibulocochlear), 263f, 275, 275f  
IX (glossopharyngeal), 263f, 276, 276f  
X (vagus), 263f, 278f, 279  
XI (accessory), 263f, 277, 277f  
XII (hypoglossal), 263f, 280, 280f  
neuron components of, 144, 144f  
and nuclei, 263–280, 263f–264f, 266f  
clinical point, 263b, 265b  
distribution of sensory, motor, and autonomic fibers, 263  
lateral view of, 266  
primordia of, 143, 143f
- CRPS. *see* Complex regional pain syndrome (CRPS)
- Crush injury, in spinal cord, 238b
- CT (computed tomography) scans, coronal and sagittal, 60, 60f
- Cuneus, 55f  
apex of, 58f
- Cutaneous nerves  
femoral  
and lateral, 193, 193f  
posterior, 195, 195f  
of head and neck, 176, 176f

- Cutaneous receptors, of peripheral nerve, 166, 166f
- Cytokines, and influences on hypothalamus and other brain regions, 435, 435b, 435f
- D**
- Dandy-Walker syndrome, 149b
- Decerebration, in vestibulospinal tracts, 403b
- Decorticate posturing, 420b
- Decussation, of pyramids, 248f
- Deep cerebellar nuclei, 283f, 287, 287f
- Dejerine-Klumpke paralysis, 181b
- Dejerine-Roussy syndrome, 70b
- Dejerine's syndrome, 73b
- Demyelination
- axonal diameter and, 27b
  - clinical disorders associated with, 342b
- Dendrites, 4, 4f
- Dendritic crest synapse, 6f
- Dendritic spine synapse, 6f
- Dendritic spines, 4f
- Dendrodendritic synapse, 6f
- Denervated skeletal muscle fibers, clinical point, 392b
- Dentate gyrus, 56f, 68
- Depolarization, 20, 30f
- Depression. *see also* Behavioral pathology  
noradrenergic brain stem pathology in, 347b
- Dermal sinus, in spina bifida occulta, 151f
- Dermatome(s), 131, 131f
- distribution of, peripheral nerves in, 174, 174f. *see also* Somatic nervous system
  - of upper limb, 182, 182f
- Descending pathways, of spinal cord, 83f
- Descending upper motor neuron tracts, in spinal cord, terminations of, 406, 406f
- Diabetic neuropathy, and delayed gastric emptying, 216b
- Diaphragm, cervical muscles and, 178
- Diencephalon, 289–293. *see also*  
Hypothalamus; Pituitary gland;  
Thalamus
- adult derivatives of, 142, 142f
  - at 28 days, 134, 134f
  - at 36 days, 135, 135f
  - at 49 days, 136, 136f
  - at junction with midbrain, 261f
  - comparison of, at 5.5 weeks and adult, 140f
  - reticular nuclei in, 282
- Diffusion tensor imaging (DTI), 67
- Diffusion-weighted imaging (DWI), 67
- Diploic veins, 116, 117f
- Diurnal rhythms, hypothalamic regulation of, 425
- Dopaminergic neurons, 281
- Dopaminergic pathways, from midbrain and hypothalamus, 349, 349f
- clinical point, 349b
- Dorsal column nuclei, in brain stem, 249f
- Dorsal column system, 169
- in brain stem, color imaging of, 344f
  - and epicritic modalities, 359–361, 359f
  - clinical point, 361b
- Dorsal horn, of spinal cord, 234
- Dorsal (motor) nucleus, of CN X, 293
- Dorsal ramus, 82, 180f–181f
- Dorsal root(s), 81, 81b, 162
- Dorsal root ganglion, 7b, 129, 243f
- Dorsolateral fasciculus, 83f, 235f–239f
- Dura mater, 49
- meningeal arteries and relationship to, 94, 94f
  - venous sinuses of, 116
- Dysautonomic polyneuropathy, 214b
- E**
- Ear, development of, 147, 147f
- Ectodermal structures, and nerves, 143f
- Edinger-Westphal nucleus, 206, 264f, 422f
- in accommodation of lens, 379b
- Electrical discharges, in seizures, types of, 33–34, 33f
- Electroencephalography (EEG), 31–32, 32f
- Electromyography, 28
- Embolic strokes, 102, 105b
- Emissary veins, 116, 117f
- Encephalocele, 152, 152f
- Endogenous opiates, 364b
- Endogenous stem cells, 14, 14f
- Enkephalin interneurons, 364b
- Enkephalins, 201
- Enteric nervous system
- cross-sectional view, 222, 222b, 222f
  - longitudinal view, 221, 221f
- Entorhinal cortex, 349f, 451, 451f
- afferent and efferent connections of, 454, 454f
  - inputs to, 452f–453f
- Epicritic modalities, dorsal column system and, 359–361, 359f
- Epicritic sensation
- afferent, clinical point, 356b
  - dorsal column system and, clinical point of, 361b
  - loss of, 234b, 236b
- Epicritic trigeminal projections, in trigeminal sensory system, 365
- Epidural hematoma, 49–50, 94
- Epidural space, 82, 124b
- Epinephrine, 449, 449f
- Epineurium, 157
- Epithalamic commissure. *see* Posterior commissure
- EPSP (excitatory postsynaptic potential), 22, 22f–23f
- Epstein-Barr syndrome, 82b
- Erb-Duchenne palsy, 181b
- Erectile dysfunction, autonomic, 231b
- Esophagus, nerves of, 215, 215f
- Ethmoid bone, 46f
- Excitatory feedback circuits, 31
- Excitatory postsynaptic potential (EPSP), 22, 22f–23f
- Excitatory summation, 30f
- Excitatory synapse, regulation of synaptic strength at, 39, 39f
- Exogenous stem cells, 14, 14f
- Explicit memory, clinical pathology of, 453b
- Extrafusal fibers, 245b
- Extraocular nerves, and ciliary ganglion, 269, 269f. *see also* Abducens nerve (CN VI); Oculomotor nerve (CN III); Trochlear nerve (CN IV)
- Extrinsic inflammatory stimuli, inflammatory response to, 16, 16f
- Eye
- anatomy of, 379, 379f
  - anterior and posterior chambers of, 380, 380f
  - arteries and veins in, 384, 384f
  - optic chiasm in, 385, 385f
  - optic nerve in, 383, 383f
  - retinal layers in, 381, 381f
  - autonomic distribution to, 206, 206f
  - development of, 146, 146f
- Eye movements, central control of, 407, 407f
- F**
- Facial colliculus, 72b, 72f
- Facial nerve (CN VII), 207f, 209f, 263f, 394f
- clinical point, 274b
  - fibers of
    - motor, 273f
    - orbital, 267
    - parasympathetic, 273f
    - parotid, 274, 274f
    - sensory, 273f
    - sympathetic, 273f
- Falx cerebelli, 118
- Falx cerebri, 118
- Familial dysautonomia, 128b
- Fascicles, of axons, 157
- Fasciculus cuneatus, 83f, 235, 235f–236f, 239f
- Fasciculus gracilis, 83f, 235, 235f–239f
- Fast anterograde axonal transport, 17, 17f
- Fast retrograde axonal transport, 17, 17f
- Femoral nerve, 193
- posterior, 195, 195f
- Fenestrated vasculature, of brain, 436, 436b
- Fibrous astrocytes, 9
- Fight-or-flight response, 448, 448f
- Filum terminale, 80
- Fissure, brain, 52
- Flaccid paralysis, 392b
- Flexor reflex interneuron, 243f
- Flexor withdrawal reflex, 244f, 357, 357f
- Follicle-stimulating hormone (FSH), 426, 438f, 439, 439b
- Food intake, signaling systems involved in regulation of, 447, 447f
- Foramina
- in base of adult skull, 47, 47f
  - clinical point, 47b
  - of ventricles, 86
- Forebrain
- adult derivatives of, 142, 142f
  - axial (horizontal) sections of
    - at anterior commissure and caudal thalamus, 304, 304f–305f



Forebrain (*Continued*)

- at basal ganglia and internal capsule, 308, 308f–309f
- at centrum semiovale, 314, 314f–315f
- at corpus callosum, 312, 312f–313f
- at dorsal caudate, splenium, and genu of corpus callosum, 310, 310f–311f
- at head of caudate and midthalamus, 306, 306f–307f
- at mid pons level, 296, 296f–297f
- at midbrain level, 300, 300f–301f
- at rostral midbrain and hypothalamic level, 302, 302f–303f
- at rostral pons level, 298f–299f, 299
- coronal sections of
  - at amygdala/anterior limb of internal capsule, 322, 322f–323f
  - at anterior commissure/columns of fornix, 320, 320f–321f
  - at caudal pulvinar and superior colliculus, 332, 332f–333f
  - at caudate nucleus/nucleus accumbens, 318, 318f–319f
  - at geniculate nuclei, 330, 330f–331f
  - at genu of corpus callosum, 316, 316f–317f
  - at mammillary body, 324, 324f–325f
  - at mammillothalamic tract/substantia nigra, rostral hippocampus, 326, 326f–327f
  - at midthalamus, 328, 328f–329f
  - at splenium of corpus callosum, 334, 334f–335f
- development of, 134, 134f
  - at 7 weeks through 3 months, 137, 137f
- hippocampal formation in, 451. *see also* Hippocampal formation
- horizontal sections of, 64
- hypothalamic regions of, 429, 429f. *see also* Hypothalamus
- lateral surface anatomy of, 52, 52f
  - Brodman's areas in, 54, 54f
  - functional regions in, 53, 53f
- limbic structures of, 65, 65f
- medial surface anatomy of, 55, 55f
- neurotransmission in, and brain stem
  - central cholinergic pathways, 350, 350f
  - dopaminergic pathways, 349, 349f
  - noradrenergic pathways, 347, 347f
  - serotonergic pathways, 348, 348f
- ventricular anatomy in, 87. *see also* Ventricles
- Fornix, 65b, 68, 68f, 292f
  - in coronal section of forebrain, 320, 320f–321f
  - in medial view, 55f
- Fourth (4th) ventricle, 55f
  - clinical point in, 72b
  - development of, 150, 150f
- Free nerve ending, 166f
- Frontal bone, 46f
- Frontal encephalocele, 152f
- Frontal eye fields, 53f
- Frontal lobe, 52f
  - medial surface of, 57f
- Frontal pole, 58f

FSH. *see* Follicle-stimulating hormone (FSH)  
Funiculus, 83, 83b

**G**

- G-protein coupled metabotropic glutamate receptors (mGluRs), 39
- G protein-coupled receptors, 25f–36f
- Galen, great cerebral vein of, 118, 120
- Gallstones, development of, 223b
- Gamma motor neurons, 246, 246f, 392, 392f
  - classification of axons of, 27f–30f
- Gemmules, 4f
- Geniculate ganglion, 203
  - of facial nerve, 264f
- Geniculate nuclei
  - clinical point, 330b
  - in coronal section, 330, 330f–331f
- GH. *see* Growth hormone (GH)
- Glabrous skin, receptors in, 166
- Glaucoma, and optic nerve damage, 380b
- Glial cell, 8. *see also* Astrocytes; Microglia; Oligodendrocyte(s)
- Glial cell-line derived neurotrophic factor (GDNF), 12f
- Glial process, 4f
- Glioblast, 133
- Gliotransmitters, 9
- Global aphasia, 346f
- Globus pallidus, 416, 416f
  - afferents to, 283f
- Glossopharyngeal nerve (CN IX), 203f, 263f, 276, 394f
  - clinical point, 276b
- Glucagon secretion, 224
- Glucocorticoid, in regulation of neurons and apoptosis, 41, 41f
- Glutamate, 39, 201
- Golgi apparatus, 4, 4f
- Golgi cells, 410, 410f
- Golgi tendon organ reflex, 357, 357f
- Gonadotropin-releasing hormone (GnRH), 426
- Graded potentials, 6
  - in neurons, 22
- Granule cells, 410, 410f
- Gray matter
  - of spinal cord, 83, 83f, 234, 393f
    - at cervical level, 235
    - at lumbar level, 235
    - at sacral level, 235
    - at thoracic level, 235
  - development of, 145, 145f
  - lower motor neuron organization and control, 243
  - neuronal cell groups, 234
  - somatic reflex pathways, 244
- Gray rami communicantes, 191f
- Gray ramus communicans, 156f, 206f, 228f–229f, 231f–232f, 422f
- Growth hormone (GH), 426, 438f, 439, 439b
- Guillain-Barré syndrome (GBS), 82b, 179b, 265b
- Gyri, of brain, 52
  - in medial view, 55f
  - topographic organization of, 53b
- Gyrus rectus, 55f

**H**

- Habenula, 283f
- Habenular commissure, 55f
- Hair cells
  - in organ of Corti, 371, 371b, 371f
  - in vestibular apparatus, 370
  - in vestibular receptors, 376
- Hair follicles, innervation of, 210
- Hairy skin, receptors in, 166
- Hallpike maneuver, 370b
- Hallux, 131
- Head, pain-sensitive structures of, 366, 366f
- Head and neck
  - autonomic distribution to
    - lateral view, 204, 204f
    - medial view, 203, 203f
    - schematic, 205, 205f
  - bony framework of, 48, 48f
  - cutaneous nerves of, 176, 176f
- Hearing loss, 369b
- Heart
  - autonomic neuropathies and, 213b
  - innervation of, 213, 213f
- Hematoma, 50, 50f
- Hemorrhagic strokes, 102
- Hepatic triad, 223f
- Herniated disc, 79
- Herniation
  - cervical disc, 183, 183f
  - lumbar disc, 161, 161f
- Heubner, artery of, 100b
- Hindbrain. *see also* Metencephalon; Myelencephalon
  - adult derivatives of, 142, 142f
- Hippocampal formation, 68, 68f, 451, 453b
  - afferent and efferent connections in, 453, 453f
  - anatomy of, 451, 451f
  - clinical point, 451b–452b
  - fimbria of, 56f, 451f
  - information processing in, 65b
  - neuronal connections in, 452, 452f
  - temporal lobe and, 452b
- Hippocampus, rostral, in coronal section, 326, 326f–327f
- Hirschsprung's disease, 128b
- Histamine, 201
- Holoprosencephaly, 136b
- Homeostasis, autonomic maintenance of, 200b
- Homunculus, 359–361
- Horizontal cell neuron, 337f
- Horizontal (lateral) gaze center, 282
- Horner's syndrome, 236b, 251b
- Hunger, neural control of, 446, 446f
- Huntington's disease, 304b, 308b
- Hydrocephalus, 89b, 91, 149b
- Hyperpolarization, 20
- Hyperreflexic responses, 35b
- Hypertonic state, 35b
- Hypoglossal nerve (CN XII), 263f, 280, 280f
  - clinical point, 280b
  - ipsilateral, clinical point in, 73b
- Hypoglossal (XII) nucleus, 394f
- Hypophyseal portal vasculature, 437, 437f
- Hypopituitarism, 439b

- Hypothalamic nuclei, 291*f*  
 clinical point, 293*b*  
 illustration of, 292*f*, 293
- Hypothalamic-pituitary-adrenal (HPA) axis, 41
- Hypothalamic sulcus, 55*f*
- Hypothalamo-pituitary-adrenal (HPA) axis, 448, 449*b*
- Hypothalamo-pituitary-adrenal system, 293*b*
- Hypothalamus, 55, 142, 291*f*. *see also* Pituitary gland  
 afferent pathway associated with, 283*f*, 430, 430*b*, 430*f*  
 schematic diagram of, 431, 431*f*  
 anatomy of, 424, 424*f*  
 appetite and hunger, 446, 446*f*  
 autonomic and endocrine regulation by, 291, 293*b*  
 axial (horizontal) sections of, MRI of, 302, 302*f*–303*f*  
 cardiac function and, 443, 443*f*  
 clinical point, 293*b*, 425*b*, 427*b*  
 connections of, 433, 433*f*  
 cytokine influences in, 435, 435*b*, 435*f*  
 dopaminergic pathways from, 349, 349*f*  
 clinical point, 349*b*  
 efferent pathway associated with, 283*f*, 430, 430*b*, 430*f*  
 schematic diagram of, 432, 432*f*  
 fight-or-flight response, 448, 448*f*  
 forebrain regions associated with, 429, 429*f*  
 and limbic structures, 65*b*, 450  
 long-term blood pressure, 445, 445*f*  
 mammillary zone of, 427, 427*f*  
 neuroimmunomodulation and, 449, 449*f*  
 nuclei located within, 282*f*, 291*f*–292*f*, 293, 293*b*, 424  
 paraventricular nucleus of, 434, 434*b*, 434*f*  
 preoptic and supraoptic zones of, 425, 425*f*  
 regulation by, 426*b*  
 diurnal and circadian rhythm, 425*b*  
 of food intake, body weight, and metabolism, 447, 447*f*  
 releasing factors secretion, 426*b*  
 sleep-wake cycle, 425*b*  
 retinal projections to, 386, 386*f*  
 schematic reconstruction of, 428, 428*f*  
 short-term blood pressure, 444, 444*f*  
 thermoregulation and, 442, 442*f*  
 tuberal zone of, 426, 426*f*  
 vascular supply to, 112, 112*f*
- I**
- Immune system, autonomic innervation of, 199, 199*f*, 222
- Inferior colliculi, 55*f*, 69, 258*f*
- Inferior longitudinal fasciculus, 344*f*
- Inferior olive, 251*f*
- Inferior sagittal sinus, 118
- Inferior temporal gyrus, 58*f*
- Inferior temporal sulcus, 58*f*
- Inflammatory cytokines, and influences on hypothalamus and other brain regions, 435*b*
- Inhibitory postsynaptic potential (IPSP), 22, 22*f*–23*f*
- Inhibitory synapses, 29
- Insula, 52
- Insular cortex, 283*f*
- Insulin-like growth factor 1 (IGF-1), 12*f*
- Insulin secretion, 224
- Interleukin-1 beta, sleep-wakefulness control and, 284
- Intermediate gray, 234
- Internal capsule (IC), 296  
 in axial (horizontal) section, 308, 308*f*–309*f*  
 clinical point, 326*b*  
 corona radiata and, 344*f*  
 in coronal section, 322, 322*f*–323*f*
- Internal carotid artery (ICA), 95, 95*b*  
 circulation, angiographic anatomy of, 108, 108*f*  
 ophthalmic arteries and, 97, 97*f*
- Internal jugular vein, 121
- Interneurons, 7, 244*f*
- Interoceptors, 168, 168*f*
- Interpeduncular nucleus, 282*f*
- Interstitiospinal tract, 405, 405*b*, 405*f*
- Interthalamic adhesion, 55*f*
- Interventricular foramen. *see also* *Monro*, foramen of  
 in midsagittal view, 55*f*
- Intervertebral discs, 78, 78*f*  
 herniation of, 81*b*
- Intracerebral hemorrhage, hypertensive, 102
- Intrafusal fibers, 245*b*
- Intralaminar nuclei, 282*f*
- Intramural ganglia, 165, 198, 422*f*, 423
- Intrinsic damage, inflammatory response to, 16, 16*f*
- Ionotropic receptors, 25*f*–36*f*
- Ipsilateral flaccid paralysis, 114
- Ipsilateral hypoglossal nerve, clinical point in, 73*b*
- Ipsilateral medial lemniscus, clinical point in, 73*b*
- Ipsilateral pyramid, clinical point in, 73*b*
- Ipsilateral spastic paralysis, 114
- IPSP (inhibitory postsynaptic potential), 22, 22*f*–23*f*
- Ischemic episode, neuronal damage in, 4
- Ischemic strokes, 102
- Isodendritic neurons, 7*b*
- J**
- Joint receptors, 245
- K**
- Kidneys, and upper ureters, autonomic innervation of, 228, 228*f*
- Klüver-Bucy syndrome, 455*b*
- Korsakoff amnesic syndrome, 427*b*
- L**
- Lacunar infarcts, 105
- Lamina 7 nuclei, 282*f*
- Lamina terminalis, 55*f*, 58*f*
- Laminae of Rexed, 234  
 at cervical level, 235  
 at lumbar level, 235  
 at sacral level, 235  
 at thoracic level, 235
- Large intestine  
 innervation of, Enteric nervous system autonomic, 218, 218*f*  
 nerves of, 220, 220*f*
- Lateral basal nucleus, 234*f*
- Lateral corticospinal tract, 83*f*, 235*f*–240*f*, 236*b*, 242*f*
- Lateral funiculus  
 clinical point, 236*b*, 358*b*  
 dorsal and ventral spinocerebellar pathways in, 358
- Lateral geniculate body, 58*f*, 264*f*  
 and nuclei of thalamus, 290*f*
- Lateral horn, 83
- Lateral hypothalamic area (LHA), 283*f*, 424*f*, 425
- Lateral medullary syndrome, 251*b*, 262*f*
- Lateral occipitotemporal gyrus, 56*f*, 58*f*
- Lateral pontine syndrome, 256*b*, 262*f*
- Lateral reticulospinal tract, 83*f*
- Lateral (sylvian) fissure, 53*f*, 58*f*
- Lemniscal channels, 163, 163*f*
- Lenticulostriate arteries, 101
- Lentiform nucleus, 64*f*
- Levetiracetam, 33*f*
- LH. *see* Luteinizing hormone (LH)
- Ligand-gated ion channels, 25*f*–36*f*  
 in neurotransmitter release, 37, 37*f*
- Limb rotation, in nervous system development, 131, 131*f*
- Limbic cingulate cortex, 57*f*
- Limbic forebrain, 65, 65*f*  
 afferent and efferent connections in, 283*f*  
 amygdala in, 457. *see also* Amygdala  
 anatomy of, 450, 450*f*  
 cingulate cortex of, 459  
 clinical point in, 65*b*  
 hippocampal formation in, 451. *see also* Hippocampal formation
- Limbic lobe, medial surface of, 57
- Lingual gyrus, 55*f*–56*f*, 58*f*
- Lissencephaly, 138*b*
- Liver  
 autonomic innervation of, 223, 223*f*  
 clinical point, 223*b*
- LMNs. *see* Lower motor neurons (LMNs)
- Lobes, of brain, 52  
 medial surface of, 57*f*
- Local anesthesia, blocking of action potential by, 25*b*
- Locus coeruleus, 282*f*  
 noradrenergic neurons in, 347
- Long-term potentiation, 453*b*
- Lower limbs, somatic innervation of  
 cutaneous femoral nerve in, 193, 193*f*  
 obturator nerve, 194, 194*f*  
 peroneal nerve in, 197, 197*f*  
 sciatic and posterior femoral nerves, 195, 195*f*  
 tibial nerve, 196, 196*f*
- Lower motor neuron (LMN) syndrome, 392*b*

- Lower motor neuron palsies, 266b  
 Lower motor neurons (LMNs), 83b, 164, 164f, 234, 392–394  
   alpha and gamma, 245b, 246, 392, 392f  
   clinical point, 6b–7b, 249b, 266b  
   development of, 129  
   distribution of  
     in brain stem, 265, 394, 394f  
     in spinal cord, 393, 393f  
   sensory nerve channels to, 162  
   in somatic reflex actions and pathways, 357  
   somatic reflex pathways, 244  
   synaptic endings of, 35b  
 Lumbar cistern, 78, 80, 80b, 91, 241, 241f  
 Lumbar disc herniation, 161, 161f  
 Lumbar plexopathy, 191b  
 Lumbar plexus, 191, 191f  
 Lumbar spinal cord, gray matter organization in, 235  
 Lumbar vertebrae  
   arteries surrounding spinal cord and, 113f  
   radiography of, 79, 79f  
 Luschka, foramina of, 86, 88, 149b  
   obstruction of, 89b  
 Luteinizing hormone (LH), 426, 438f, 439, 439b  
 Lysosome, 4f
- M**  
 M1-M3 muscarinic receptors, 423b  
 Magendie, foramen of, 86, 88, 149b  
   obstruction of, 89b  
 Magnetic resonance angiography, of brain  
   arterial system, frontal and lateral views, 107, 107f  
 Magnetic resonance imaging (MRI)  
   functional, of cerebral cortex, 345, 345f  
   high-resolution axial sections  
     at anterior commissure and caudal thalamus, 304f–305f  
     at basal ganglia and internal capsule, 308f–309f  
     at centrum semiovale, 314f–315f  
     at corpus callosum, 312f–313f  
     at dorsal caudate, splenium, and genu of corpus callosum, 310f–311f  
     at head of caudate and midthalamus, 306f–307f  
     at mid pons level, 296, 296f–297f  
     at midbrain level, 300f–301f  
     at rostral midbrain and hypothalamic level, 302f–303f  
     at rostral pons level, 298f–299f  
   high-resolution coronal sections  
     at amygdala/anterior limb of internal capsule, 322f–323f  
     at anterior commissure/columns of fornix, 320f–321f  
     at caudal pulvinar and superior colliculus, 332f–333f  
     at caudate nucleus/nucleus accumbens, 318f–319f  
     at geniculate nuclei, 330f–331f  
     at genu of corpus callosum, 316f–317f  
   Magnetic resonance imaging (MRI)  
     (Continued)  
     at mammillary body, 324f–325f  
     at mammillothalamic tract/substantia nigra, rostral hippocampus, 326f–327f  
     at midthalamus, 328, 328f–329f  
     at splenium of corpus callosum, 334f–335f  
   T1-weighted  
     of brain, axial and sagittal views, 61, 61f  
     of brain stem, caudal to rostral cross-sections, 248  
   T2-weighted  
     of brain, axial and sagittal views, 62, 62f  
     of spinal cord, sagittal sections, 241  
     of ventricles, axial and coronal views, 90, 90f  
 Mammillary body, 55f–56f, 58f  
   in coronal section, 324, 324f–325f  
 Mammillary peduncles, 283f  
 Mammillothalamic fasciculus, 56f  
 Mammillothalamic tract, in coronal section, 326, 326f–327f  
 Mandibular nerve (V<sub>3</sub>), 176f, 270f, 271  
 Maxillary nerve (V<sub>2</sub>), 208f, 270f, 271  
 Medial basilar infarct, 262f  
 Medial frontal gyrus, 55f  
 Medial geniculate body, 58f  
   in cross-section, 260f  
   and nuclei of thalamus, 290f  
 Medial inferior pontine syndrome, 253b  
 Medial lemniscus, ipsilateral, clinical point in, 73b  
 Medial longitudinal fasciculus, 83f, 235f–238f  
 Medial medullary syndrome, 262f  
 Medial midbrain syndrome, 262f  
 Medial occipitotemporal gyrus, 56f, 58f  
 Medial pontine syndrome, 262f  
 Median eminence, 436, 436b, 436f  
 Median forebrain bundle, 283f, 292f  
 Median nerve, 188, 188f  
   compression of, 189  
 Medulla, 142  
   arterial syndromes of, 262f  
   axial anatomy of  
     at genu of facial nerve, 255f  
     at level of CN X and vestibular nuclei, 252f  
     at level of cochlear nuclei, 253f  
     at level of dorsal column nuclei, 249f  
     at level of facial nucleus, 254f  
     at level of inferior olive, 251f  
     at level of obex, 250f  
     at pontine junction, 253f  
     at spinal cord transition area, 248f  
   clinical point  
     bulbar palsy and pseudobulbar palsy, 249b  
     lateral medullary syndrome, 251b  
     medial inferior pontine syndrome, 253b  
   comparison of, at 5.5 weeks and adult, 140f  
 Medulla (Continued)  
   lateral reticular formation of, 282f  
   nuclei, 282  
 Megacolon, chronic, clinical point, 222b  
 Meissner's plexuses, 221  
 Melanocyte-stimulating hormone (MSH), 438f, 439  
 Meningeal arteries, 94  
   tear in, hematoma and, 50  
 Meningeal veins, 116, 117f  
 Meninges  
   arterial system of, 95, 95f  
     and relationship to skull and dura, 94, 94f  
   of brain, 49, 49f  
   of spinal cord, 81  
 Meningocele, 151, 151f  
 Meningomyelocele, 127b, 151, 151f  
 Merkel's discs, 166  
 Mesencephalic reticular formation, 349  
 Mesencephalon. *see also* Midbrain  
   adult derivatives of, 142f  
   at 28 days, 134, 134f  
   at 36 days, 135, 135f  
   at 49 days, 136, 136f  
   comparison of, at 5.5 weeks and adult, 140f  
 Metabolic cells, neuroeffector junctions of, 173  
 Metabolic organs, autonomic innervation of, 199, 199f  
 Metabolic syndrome, chronic stressors and, 223b  
 Metabolism, signaling systems involved in regulation of, 447, 447f  
 Metabotropic receptors, 25f–36f  
   in neurotransmitter release, 37, 37f  
 Metencephalon, 135, 135f  
   adult derivatives of, 142f  
   at 49 days, 136, 136f  
   myelencephalon, 142f  
 N-methyl-D-aspartate receptor (NMDAR), 39  
 Meyer's loop, and visual loss, 388b  
 Microglia, 8, 133  
   biology of, 10, 10f  
 Microgyria, 138b  
 Microneuron, 4  
 Midbrain. *see also* Mesencephalon  
   adult derivatives of, 142, 142f  
   arterial syndromes of, 262f  
   axial anatomy of, 300, 300f–301f  
     at level of inferior colliculus, 258f  
     at level of medial geniculate body, 260f  
     at level of superior colliculus, 259f  
   clinical point, 258b, 260b, 300b  
   dopaminergic pathways from, 349, 349f  
     clinical point, 349b  
   lateral reticular formation of, 282f  
   nuclei of, 282  
 Midbrain colliculi, 55  
 Middle cerebral artery (MCA)  
   basal view of, 98  
   coronal forebrain section, 101, 101f  
   in frontal view, 100  
   lateral and medial views of, 105  
   territory of, colored illustration, 106, 106f



- Midline nuclei, 282f  
Miosis, 236b  
Mitochondrion, 4, 4f  
Monoamine oxidase inhibitors, 347b  
Monosynaptic reflex channels, 162  
Monro, foramen of, 86, 89  
Mossy fibers, 410–411, 410f–411f  
Motor cortex, 53f  
  corticobulbar, 397  
  corticospinal, 399  
  efferent pathways of, 395  
  functional magnetic resonance imaging of, 345f  
Motor fibers, in thorax, 180  
Motor nerve fibers, of cranial nerves, 263  
Motor neuron(s), 5f. *see also* Lower motor neurons (LMNs); Motor nerve fibers; Upper motor neurons (UMNs)  
  classification of axons of, 27f–30f  
  development of, 145, 145f  
  myelination of axons of, 18  
  schematic representation of, 243f  
Motor systems, 391–419  
  basal ganglia in, 416–419. *see also* Basal ganglia  
  cerebellum in, 409–415. *see also* Cerebellum  
  lower motor neurons in, 392–394. *see also* Lower motor neurons (LMNs)  
  upper motor neurons in, 395–408. *see also* Upper motor neurons (UMNs)  
Motor units, 392b  
Movement disorders, 304b, 308b, 416b  
MSH. *see* Melanocyte-stimulating hormone (MSH)  
Multipolar cell, 7f  
Multisensory association areas, of cortex, 53f  
  basal surface of, 59f  
Muscarinic receptors, 202  
  M1-M3, 423b  
Muscle spindles, 245  
  detail of, 245f  
Muscle stretch reflex, 357, 357f  
  clinical point, 246b, 356b  
Muscular dystrophy (MD), 172b  
Musculocutaneous nerve, 187, 187f  
Myasthenia gravis, 170b  
*Mycoplasma pneumoniae*, 82b  
Myelencephalon, 135, 135f  
  at 49 days, 136, 136f  
Myelin sheath, in neuronal function, 18b  
Myelinated axon, 18, 157  
  action potential in, 25  
  conduction of action potentials in, 26, 26f  
Myelinated fibers, 7f  
Myelination, 18  
  development of, 19, 19f  
  triggering of, by axonal diameter, 27b  
Myenteric plexus, 221
- N**  
Nasal cavity, autonomic innervation of, 207, 207f  
Near vision, pupillary regulation in, 204
- Neocortex, cell migration in, 139, 139f  
Nerve growth factor (NGF), 12f  
Nerve roots, 81  
Nervous system  
  autonomic-hypothalamic-limbic systems, 421–461. *see also* Autonomic-hypothalamic-limbic systems  
  central  
    brain in, 51–70. *see also* Brain  
    brain stem and cerebellum in, 71–75. *see also* Brain stem; Cerebellum  
    spinal cord in, 77–83, 233–246. *see also* Spinal cord  
    ventricles and cerebrospinal fluid in, 91. *see also* Cerebrospinal fluid (CSF); Ventricles  
  cranial nerves of, 263–280. *see also* Cranial nerves  
  motor systems of, 391–419. *see also* Basal ganglia; Cerebellum; Lower motor neurons (LMNs); Upper motor neurons (UMNs)  
  neurons in, 1–43. *see also* Neurons  
  peripheral, 153–232. *see also* Peripheral nervous system (PNS)  
  sensory systems of, 353–390. *see also* Sensory systems  
  skull and meninges of, 45–50. *see also* Meninges; Skull  
  vasculature of, 93–124. *see also* Arterial system; Venous system  
Nervus intermedius, 263f  
Neural crest  
  derivatives of, 133, 133f  
  formation of, 126, 126f  
  and neural tube development, 128, 128f  
Neural plate  
  in 21- or 22-day-old-embryo, 127  
  formation of, 126, 126f  
Neural proliferation, and differentiation, 132, 132f, 139  
Neural tube  
  at 5 weeks, 132f  
  defects of, 151, 151f  
  derivatives of, 133, 133f  
  development, 128, 128f  
  formation of, 126, 126f  
  walls of, 132, 132f  
Neurilemmal cells. *see* Schwann cells  
Neuroblasts, 133  
Neurodegenerative process, response to, 16, 16f  
Neuroendocrine regulation  
  by hypothalamus, 293b  
  of pituitary gland, 293b  
Neuroepithelial progenitor cells, 139  
Neurogenesis, 139, 139f  
Neurohypophyseal hormones, 440, 440f  
Neurohypophysis, 291f  
Neuroimmunomodulation, 449, 449f  
Neuromediators, 201  
Neuromuscular junction, 129, 170, 170f  
  pharmacology of, 172, 172f  
  physiology of, 171, 171f
- Neurons  
  action potentials of, 24, 24f. *see also* Action potentials, neuronal  
  cortical  
    electrical firing patterns of, 31, 31f  
    types of, 337, 337f  
  current flow in, 22f  
  differentiation of  
    in 5 to 7 week embryo, 129f  
    in 26–28 day embryo, 129f  
  energy and metabolic requirements of, 4b  
  forms and functions of, 7  
  glial cell types in, 8. *see also* Glial cell  
  glucocorticoid regulation of, 41, 41f  
  graded potentials in, 22  
  growth factors and trophic factors of, 12, 12f  
  inhibitory and excitatory, 30  
  membrane potential and sodium channels in, 21, 21f  
  molecular signaling in, mechanisms of, 25f–36f, 36  
  properties of, 1–43  
    anatomical and molecular, 4–19  
    electrical, 20–34  
  resting potential in, 20, 20f  
  signal transduction of, 39, 39f–40f  
  structure of, 4, 5f  
  summation of input to, 30  
  synapses of, 6. *see also* Synapses  
  types of, 7  
Neuropathic pain, mechanisms of, 363–364, 363f  
Neuropathies, diagnosis of, 28  
Neuropeptides, 43, 201  
Neurotransmission  
  at cholinergic synapses, 201  
  chemical, 42f, 43  
  and neuromuscular junction, 170, 170f  
Neurotransmitter-receptor mismatch, 38, 38f  
Neurotransmitter(s), 6  
  acetylcholine, 164. *see also* Acetylcholine  
  amino acid, 43  
  chemical, synaptic morphology in, 35  
  co-localization and release of, 38f  
  excitatory and inhibitory, 22  
  multiple, 38, 38f  
  non-linearity of release of, 38f  
  norepinephrine, 201. *see also* Norepinephrine  
  preganglionic and postganglionic, 423b  
  release, 37, 37f  
  and signaling properties, 35–43  
Neurotubules, 4f  
Neurulation, 127, 127f  
  failure of, 127b  
Nicotinic cholinergic receptors, 423b  
Nicotinic receptors, 164, 201–202  
Nitric oxide, 215  
Nociceptive axons  
  descending control of ascending, 364  
  in spinothalamic and spinoreticular systems, 361–362  
  clinical pathology of, 361b  
  spinal cord processing of, 362–363, 362f  
  trigeminal, 365

Node of Ranvier, 18  
 Nodose ganglion, 203  
 Noradrenergic pathways, in brain stem, 347, 347f  
     clinical point, 347b  
 Norepinephrine, 43, 173, 423b, 449, 449f  
 Nose, nerves of, 352, 352f  
 Notochord, 126  
 Nuclear cell columns, of spinal cord, 234f  
 Nuclear signaling, regulation of, 40, 40f  
 Nucleolus, 4f  
 Nucleus, 4f  
 Nucleus accumbens  
     connections of, 419, 419f  
     coronal section through, 318, 318f–319f  
     dopaminergic neurotransmission in, and associated emotions and behavior, 318b, 349b  
 Nucleus ambiguus, 264f, 277b, 394  
 Nucleus basalis (of Meynert), cholinergic pathways originating in, 350  
 Nucleus dorsalis of Clarke, 236f–237f  
 Nucleus posterior marginalis, 234f  
 Nucleus proprius, of posterior horn, 234f  
 Nucleus pulposus, herniated, impingement of, 78  
 Nystagmus, 370b, 378, 378f  
     clinical point, 420b

## O

Obesity, clinical point, 217b  
 Obex, cross-sectional anatomy of medulla at, 250f  
 Obturator nerve, 194, 194f  
 Occipital bone, 46f  
 Occipital encephalocele, 152f  
 Occipital lobe, 52f  
     medial surface of, 57f  
 Occipital pole, 58f  
 Occipital-temporal association fibers, 343f  
 Occipitofrontal fasciculi, superior and inferior, 342f  
 Occipitotemporal sulcus, 56f, 58f  
 Oculomotor control, 407  
 Oculomotor nerve (CN III), 263f, 394f  
     and ciliary ganglion, 269, 269f  
     clinical point, 73b, 203b, 268b, 379b  
     fibers of, in orbit, 267  
 Olfactory bulb, 58f–59f  
     clinical point, 58b, 461b  
 Olfactory cortex, 59f, 461  
 Olfactory nerve (CN I), 263f  
     and projections into CNS, 352, 352f  
     clinical point, 352b  
 Olfactory pathways, 461, 461f  
 Olfactory receptors, 460, 460f  
     clinical point, 352b, 460b  
 Olfactory sulcus, 58f  
 Olfactory tract, 58f–59f  
     clinical point, 461b  
 Oligodendrocyte(s), 7f–8f  
     biology of, 11, 11f  
     central myelination of axons of, 18  
     precursor cells, 11  
 Oligodendroglial progenitor cells, 13  
 Olivopontocerebellar atrophy, 412b

Ophthalmic artery, and internal carotid, 97, 97f  
 Ophthalmic nerve, 176f, 270f, 271  
 Opioid analgesia, central nervous system, 364b  
 Optic chiasm, 55f, 58f–59f, 385, 385f  
     clinical point, 58b  
 Optic cup, 146  
 Optic nerve (CN II), 263f, 267, 383, 383f  
     clinical point, 267b  
     glaucoma in, 380b  
     visual field deficit resulting from, 386b  
     and optic chiasm, 385  
     and retina, 383  
     retinal cell axons passing via, 381f  
 Optic recess, 55f  
 Optic tract, 58f–59f  
     clinical point in, 58b  
 Orbit  
     development of, 146, 146f  
     nerves of, 267, 267f–268f  
 Orbital gyri, 58f  
 Orbital sulcus, 58f  
 Organ of Corti, 371, 371f  
     clinical point, 371b  
 Organum vasculosum of the lamina terminalis (OVLT), 425, 436, 436b, 436f  
 Otic ganglion, 203, 422f  
     schematic of, 209, 209f  
 Oxytocin, 440, 440f

## P

Pachygyria, 138b  
 Pacinian corpuscles, 167, 167f  
 Pain modulation, endogenous and exogenous, 364  
 Pain referral, pain-sensitive structures of head and, 366, 366f  
 Paleocerebellum, 74b  
 Pallidotegmental tract, 283f  
 Pallidothalamic connections, 418  
 Pancreas, autonomic innervation of, 224, 224f  
 Papez circuit, 65b  
 Parabrachial nucleus, 282f  
 Paracentral lobule, 55f, 57f  
 Parahippocampal gyrus, 56f, 58f  
 Paramedian midbrain syndrome, 262f  
 Paraneoplastic syndrome, 413b  
 Parapontine reticular formation, 282f  
 Parasympathetic nervous system (PsNS), 165.  
     *see also* Autonomic nervous system  
     distribution of, 202, 202f  
     in abdomen, 214  
     in eye, 206  
     in head and neck, 203  
     in immune system and metabolic organs, 199, 199f  
     in kidneys, ureters, and urinary bladder, 228, 228f  
     in kidneys and upper ureter, 229, 229f  
     in limbs, 210, 210f  
     in liver and biliary tract, 223, 223f  
     in nasal cavity, 207, 207f  
     in otic ganglia, 209, 209f  
     in pancreas, 224, 224f  
     in pelvic region, 227, 227b, 227f  
 Parasympathetic nervous system (PsNS) (Continued)  
     in pterygopalatine and submandibular ganglia, 208, 208f  
     in small and large intestines, 218, 218f  
     in stomach and duodenum, 216, 216f  
     in tracheobronchial tree, 212, 212f  
     postganglionic neurons of, 423b  
     preganglionic neurons of, 423b  
 Paraterminal gyrus, 55f  
 Paraventricular nuclei (PVN), 291, 293b, 425  
     in neuroimmunomodulation, 449b  
     regulation of, in hypothalamus, 434, 434b, 434f  
 Paravertebral ganglia. *see* Sympathetic chain ganglia  
 Parietal bone, 46f  
 Parietal lobe, 52f  
     clinical point, 389b  
     medial surface of, 57f  
     visual pathways in, 389, 389f  
 Parieto-occipital sulcus, 55f  
 Parkinson's disease, 349b  
     clinical point, 417b  
 Parotid gland, facial nerve fibers in, 274, 274f  
 Paroxysmal depolarization shift (PDS), 33f  
 Pars compacta, of substantia nigra, 349, 417  
 Pars distalis, 148f  
 Pars nervosa, 148f  
 Pelvic splanchnic nerves, 130  
 Peptide synapse, 42f, 43  
 Perforated substance, anterior and posterior, 58f  
 Periaqueductal gray, 364, 364b  
 Perineurium, 157  
 Peripheral axons, development of, 129, 129f  
 Peripheral nerve(s)  
     anatomy of, 157, 157f  
     chronic compression of, 158  
     classification of, 27, 27f–30f  
     compression of, 159. *see also* Compression neuropathy  
     cutaneous distribution of, 175, 175f. *see also* Cutaneous nerves  
     cutaneous receptors, 166, 166f  
     degeneration of, in compression injury, 159. *see also* Compression neuropathy  
     destructive lesions in, 156b  
     interoceptors of, 168, 168f  
     lemniscal sensory channels of, 163, 163f  
     motor channels, 164, 164f  
     neuroeffector junctions of, 173, 173f  
     neuromuscular junctions of, 170, 170f  
     organization of, at spinal cord, 156, 156f  
     Pacinian corpuscle receptors of, 167, 167f  
     reflex and cerebellar sensory channels of, 162, 162f  
     somatic, 174–197. *see also* Somatic nervous system  
     spinal nerve roots of, and related vertebrae, 160, 160f  
 Peripheral nervous system (PNS), 153–232.  
     *see also* Peripheral nerve(s)  
     autonomic, 202, 202f. *see also* Autonomic nervous system (ANS)

- Peripheral nervous system (PNS) (*Continued*)
- autonomic channels, 165, 165f
  - axonal transport in, 17, 17f
  - cutaneous receptors, 166, 166f. *see also* Cutaneous receptors
  - development of
    - in 5 to 7 weeks, 129f
    - in 21- or 22-day-old-embryo, 127, 127f
    - in 24 day embryo, 128f
    - in 26-28 day embryo, 129f
    - development of peripheral axons in, 129, 129f
    - limb rotation and dermatomes in, 131, 131f
    - neural crest, formation of, 126, 126f
    - neural plate, formation of, 126, 126f
    - neural proliferation and differentiation, 132, 132f, 139
    - neural tube, formation of, 126, 126f
    - neurulation, 127, 127f
    - somatic *versus* splanchnic nerve development, 130, 130f
  - interoceptors of, 168, 168f
  - motor channels, 164, 164f
  - myelination of, 18, 18f
  - neuroeffector junctions in, 173
  - neuromuscular junction in, 170, 170f
  - organization of, at spinal cord, 156, 156f
  - Pacinian corpuscle receptors of, 167, 167f
  - preganglionic neurons of, 202
  - somatic, 174–197. *see also* Somatic nervous system
- Peripheral neuropathies, clinical point of, 356b
- Peroneal nerve, 197, 197f
- PET (positron emission tomography) scanning, 63, 63f
- Petrosal ganglion, 203
- Petrosal sinuses, 118b
- Pharyngeal arch cranial nerve components, 144
- Pharyngeal arches, and nerves, 143f
- Phase contrast phenomena, 107
- Photoreceptors, 382, 382f
- Phrenic nerve, 179, 179f
- clinical point, 179b
- Pia, 81
- Pia mater, 49
- Pilomotor fibers, 210
- Pineal gland, 55f, 69, 436, 436b, 436f
- Pituicytes, 148
- Pituitary gland, 55f, 57f, 291f
- anterior
    - clinical point, 439b
    - hormone secretion of, 438f, 439
  - basal view of, 58f
  - blood supply of, 437f
  - development of, 148, 148f
  - hypothalamus and, 291
  - neuroendocrine regulation of, 293b. *see also* Hypothalamus
  - posterior, 436b, 436f
    - clinical point, 440b
    - hormones by, 440, 440f
    - vascular supply to, 112, 112f
- Pituitary tumors, 439b
- Placodes, 144
- Plasticity, synaptic, 35b
- Polio, 83b
- Polysynaptic (flexor) reflexes, 243
- Pons, 55f, 57f
- arterial syndromes of, 262f
  - axial anatomy of
    - at genu of facial nerve, 255f
    - at junction with medulla, 253f
    - at junction with mid-brain, 257f
    - at level of facial nucleus, 254f
    - at level of trigeminal motor and main sensory nuclei, 256f
    - rostral, 298f–299f, 299
  - clinical point, 255b
  - lateral pontine syndrome, 256b
  - medial inferior pontine syndrome, 253b
  - pontine hemorrhage, 255b
  - lateral reticular formation of, 282f
- Pontine hemorrhage, 255b
- Pontine reticular formation, 282f
- Pontine tract, 83f
- Positron emission tomography (PET) scanning, 63, 63f
- Posterior cerebral artery (PCA)
  - in basal view, 98
  - lateral and medial views of, 105
  - territory of, colored illustration, 106, 106f
- Posterior commissure, 55f
- at level of midbrain-diencephalon junction, 261f
- Posterior cranial fossa, arteries of, 109f
- Posterior (dorsal) spinocerebellar tract, 83f
- Posterior fossa hematoma, 50f
- Posterior horn, nucleus proprius, 234f
- Posterior inferior cerebellar artery (PICA), 109
- syndrome, 262f
- Posterior perforated substance, 58f
- Posterior spinal arteries, 114, 114f
- in cross section, 115f
- Posterolateral thalamic syndrome, 70b
- Postganglionic axons, 129, 160
- autonomic
    - classification of, 27f–30f
    - myelination of, 18
- Postganglionic neurons, 156
- Postganglionic parasympathetic neurons, 423b
- Postganglionic sympathetic neurons, 423b
- Postotic somites, 143f
- Postsynaptic inhibition, 29, 29f
- Precentral sulcus, 55f, 57f
- Precuneus, 55f
- Preganglionic axon, 165
- Preganglionic neurons, 156, 165
- autonomic, 7
    - classification of, 27f–30f
    - clinical point, 7b
- Preganglionic parasympathetic neurons, 423b
- Preganglionic sympathetic neurons, 423b
- Premotor cortex, 53f
- Preotic somitomeres, 143f
- Pressure gradients, nerve compression and, 158
- Pressure sensation. *see* Epicritic sensation
- Presynaptic inhibition, 29, 29f, 357, 357f
- Primary afferents, somatosensory, 361–363
- Primary auditory cortex, 53f
- Primary motor cortex, 53f, 57f
- Primary sensory axons, 156
- in taste pathways, 368
- Primary sensory neurons, 156
- Primary somatosensory cortex, 53f
- Primary somatosensory unmyelinated afferents (C fibers), 361–363
- Primary trigeminal region, of motor cortex, 53f
- Primary visual cortex, 53f, 57f
- basal surface of, 59f
- Progressive neuronal degeneration, in cerebellum, 412b
- Projection fibers, of cerebral cortex, 339f
- color imaging of, 343–344, 343f–344f
  - neuronal origins of, 340
- Projection neurons, 7
- Prolactin (LTH), 439
- Proprioception
  - dorsal column system and, 359f
  - in trigeminal sensory system, 365f
- Proprioceptive fibers, 243f
- Prosencephalization, 136b
- Prosencephalon
  - at 28 days, 134, 134b, 134f
  - at 36 days, 135, 135f
- Protein, dietary, in mood and affective behavior, 43b
- Proteinopathy, intrinsic, response to, 16, 16f
- Protoplasmic astrocytes, 9
- Pseudobulbar palsy, 249b
- Psychiatric disorders, 349b
- Psychomotor stimulants, 347b
- Pterygopalatine ganglion, 204, 352f, 422f
- autonomic innervation through, 207
- Pulvinar, 58f
- caudal, in coronal section of forebrain, 332f–333f
- Pupillary light reflex, 203b, 206, 387, 387f
- Pure autonomic failure, 198b
- Purkinje cell neurons, 7b, 410–411, 410f–411f
- Pyramid(s)
  - decussation of, 248f
  - ipsilateral, clinical point in, 73b
- Pyramidal cell, 4, 7f
- of hippocampal formation, 451
- Pyramidal cell neurons
  - efferent connections of, 340f
  - sensitivity of, to damage, 68
  - types of, 337f
- Pyramidal tract, 83f, 344f
- Pyramidal tract syndrome, 73b
- Q**
- Quadrigeminal bodies, development of, 136
- Quantal release, neurotransmitter, 37
- R**
- Radial glia, 9
- Radial nerve
  - above the elbow, 185
  - in forearm, 186, 186f



- Radicular arteries, 113  
in cross-section of spinal cord, 115
- Rami communicantes, 81*f*  
gray, 160  
white, 160
- Raphe dorsalis, 348, 348*f*
- Raphe magnus, 348, 348*f*
- Raphe nuclei, 281*f*
- Raphe obscurus, 348*f*
- Raphe pallidus, 348*f*
- Raphe pontis, 348*f*
- Receptors  
cochlear, 372, 372*f*  
cutaneous, 166, 166*f*  
photo, 382, 382*f*  
somatosensory, 357*f*  
taste sensory, 367–368, 367*f*  
vestibular, 376, 376*f*
- Reciprocal synapse, 6*f*
- “Recovered memory”, 453*b*
- Recruitment by convergence, 362–363, 362*f*
- Recurrent inhibition, 357, 357*f*  
of tendon organ reflex, 244*f*
- Red nucleus, 58*f*, 264*f*, 292*f*, 394*f*
- Reflex evaluation, 196*b*
- Reflex pathways  
autonomic, 200, 200*f*  
somatic, in gray matter spinal cord, 244
- Reflex sympathetic dystrophy (RSD),  
363–364, 363*b*
- Remodeling, synaptic, 35*b*
- Renshaw cell bias, 244*f*, 357, 357*f*
- Respiration, central control of, 408, 408*f*  
clinical point, 408*b*
- Respiratory nuclei, 281*f*
- Resting potential, neuronal, 20, 20*f*
- Resting state, of neuron, 30*f*
- Reticular formation (RF), 281–284  
afferent and efferent connections to, 283, 283*f*  
noradrenergic neurons in, 347  
nuclei of, in brain stem and diencephalon, 282  
pattern of nuclei in brain stem, 281  
sleep-wakefulness control in, 284, 284*f*
- Reticulospinal pathways, 404, 404*f*
- Reticulospinal tracts, 420*b*  
lateral (medullary), 235*f*–238*f*
- Retina, 381  
clinical point, 381*b*  
cerebrovascular disease in, 384*b*  
complex arrays of synapses in, 6*b*  
as derivative of CNS, 134*b*  
inner plexiform layer of, 6*f*  
and optic nerve, 383, 383*f*  
photoreceptors of, 382, 382*f*
- Retino-geniculo-calcarine pathway, 388, 388*f*
- Rhinal sulcus, 56*f*, 58*f*
- Rhombencephalon. *see* Metencephalon;  
Myelencephalon
- Ribosomes, 4*f*
- Rods and cones. *see* Photoreceptors
- Rostral ventrolateral medulla (RVLM) nuclei, 282*f*
- Rough endoplasmic reticulum, 4*f*
- Rubrospinal tract, 83*f*, 237*b*, 240*f*, 401, 401*f*  
clinical point, 420*b*
- S**
- Saccular aneurysms, 104*b*
- Sacral plexopathies, 192*b*
- Sacral plexus, 192, 192*f*
- Sacral spinal cord  
clinical point, 238*b*, 241*b*  
gray matter organization in, 235
- Sacrum, 78*f*  
arteries surrounding spinal cord and, 113*f*
- Salivation, autonomic regulation of, 205*b*
- Salivatory nuclei, 205*b*, 422*f*  
superior and inferior, 264*f*
- Saltatory conduction, 11, 18, 25
- Satellite cells, 7, 18*f*
- “Satiety center”, 446*f*
- Scapular nerve, 185, 185*f*
- Schwann cells, 7, 7*f*  
myelination of axons by, 18  
unmyelinated axons in, 157
- Schwannoma, acoustic, 275*b*
- Sciatic nerve, 195
- Secondary somatosensory cortex, 53*f*
- Secretory glands, neuroeffector junctions of, 173
- Seizures  
origin and spread of, 31, 31*f*  
types of electrical discharges in, 33–34, 33*f*
- Semicircular canals, clinical point of, 370*b*
- Sensory axons, myelination of, 18
- Sensory channels  
lemniscal, 163, 163*f*  
reflex and cerebellar, 162, 162*f*
- Sensory neuron, 7, 7*f*
- Sensory nuclei, of trigeminal nerve, 256*f*
- Sensory systems, 353–390  
auditory, 369–375  
bony and membranous labyrinths, 370, 370*f*  
somatosensory, 356–364  
taste, 367–368, 367*f*  
trigeminal, 365–366, 365*f*  
visual, 379–390
- Septal nuclei, 282*f*, 283, 350, 458  
afferent and efferent connections of, 283*f*, 458, 458*f*  
central cholinergic neurons of, 350  
cholinergic neurons of, 458*b*  
and long-term traces, 458*b*
- Septum pellucidum, 55*f*
- Serial synapse, 6*f*
- Serotonergic neurons, 281
- Serotonergic pathways, in brain stem and forebrain, 348, 348*f*  
clinical point, 348*b*
- Serotonin, synapse, 42*f*, 43
- Serotonin-specific reuptake inhibitors, 348*b*
- Sex steroid hormones, and brain  
development, 426
- Sexual behavior, and ventromedial nucleus, 426
- Shingles, 420*b*
- Short-term memory, 451
- “Silent lesions”, 342*b*
- Simple synapse, 6*f*
- Sinus, confluence of, 123*b*
- Skin, peripheral nerves in, 169, 169*f*
- Skull, 45–50  
base of  
foramina in, 47, 47*f*  
interior view of, 46, 46*f*  
bony framework of, 48, 48*f*  
defects of, 152, 152*f*  
fractures of, 94  
hematoma and, 50, 50*f*  
meningeal arteries and relationship to, 94, 94*f*  
meninges and, 49, 49*f*  
sulci of, 94
- Sleep, reticular formation associated with, 284
- Sleep-wake cycle, hypothalamic regulation of, 425
- Slow anterograde axonal transport, 17, 17*f*
- Small intestine  
innervation of. *see also* Enteric nervous system  
autonomic, 218, 218*f*  
nerves of, 219, 219*f*
- Small myelinated (M) axons, 356
- Small myelinated nerve fibers (A delta fibers), 361–362
- Smooth muscle, vascular, 204
- Solitary tract nucleus, 276
- Soma (cell body), 4*f*
- Somatic nervous system  
brachial plexus, 181, 181*f*  
cervical plexus in situ, 177, 177*f*  
cutaneous nerves of head and neck in, 176, 176*f*  
dermatomal distribution of, 174, 174*f*  
development of, 130, 130*f*  
lower limb innervation  
obturator nerve, 194, 194*f*  
peroneal nerve, 197, 197*f*  
sciatic and posterior femoral nerves, 195, 195*f*  
tibial nerve, 196, 196*f*  
lumbar plexus, 191, 191*f*  
phrenic nerve, 179, 179*f*  
sacral and coccygeal plexuses in, 192, 192*f*  
thoracic nerves in, 180, 180*f*  
upper limb innervation  
median nerve, 188, 188*f*  
scapular, axillary, and radial nerves, 185, 185*f*  
ulnar nerve, 190, 190*f*
- Somatic reflex pathways, in spinal cord, 244, 357, 357*f*
- Somatopleure, 130
- Somatosensory afferents, to spinal cord, 356, 356*f*
- Somatosensory cortex, 53*f*, 57*f*  
information processing in, 163
- Somatosensory systems, 356–364  
descending control of ascending, 364, 364*f*  
dorsal column and epicritic modalities in, 359–361, 359*f*  
neuropathic pain mechanisms in, 363–364, 363*f*  
primary afferents in, 356

- Somatosensory systems (*Continued*)  
 spinal reflex in, 357  
 spinocerebellar, 358, 358f  
 spinothalamic and spinoreticular, 360f, 361–362
- Somatostatin, 201, 426
- Somites, 144  
 primordia, 143f
- Sound reception, peripheral pathways for, 369, 369f
- Sound transduction, 369  
 clinical point, 369b
- Sound waves, in organ of Corti, 371
- Spastic bulbar palsy, 249b
- Spatial excitatory summation, 30, 30f
- Sphenoid bone, 46f
- Spina bifida, 127b, 151
- Spina bifida aperta, 151f
- Spina bifida occulta, 151f
- Spinal arteries, anterior and posterior, 114, 114f
- Spinal column  
 bony anatomy of, 78  
 longitudinal growth of, 160b
- Spinal cord, 77–83, 233–246  
 in 3 months, 132f  
 afferent and efferent connections in, 283f  
 afferents to, 283f  
 anterior (ventral) view of, 81, 81f  
 arterial blood supply to  
 cross-sectional view, 115, 115b, 116f  
 longitudinal view, 113, 113f  
 comparison of, at 5.5 weeks and adult, 140, 140f  
 cross-sectional anatomy of, 239f–240f  
 in situ, 82, 82f  
 defective, 151, 151f  
 development of, 145  
 fiber tracts of, 83f  
 gray matter of, 83, 234, 393f  
 at cervical level, 235  
 at lumbar level, 235  
 at sacral level, 235  
 at thoracic level, 235  
 gross anatomy in situ, 80, 80f  
 levels of, 83, 83b, 83f  
 lower motor neuron distribution in, 393, 393f  
 lower motor neuron organization and control in, 243. *see also* Lower motor neurons (LMNs)  
 magnetic resonance imaging of, sagittal views, 241  
 meninges, 81, 81f  
 motor and preganglionic autonomic nuclei in, development of, 145, 145f  
 nuclei of medullary junction with, 282f  
 posterior (dorsal) view of, 81, 81f  
 secondary sensory processing in, 234b  
 somatic reflex pathways in, 244, 357, 357f  
 somatosensory afferents to, 356, 356f  
 spinal roots, 81f  
 venous drainage of, 124, 124f  
 white matter of, 83, 235
- Spinal cord infarct, 113
- Spinal nerve, 81f–82f, 82
- Spinal nerve roots, 160, 160f  
 relationship to vertebrae, 160, 160f
- Spinal reflex pathways, 244. *see also* Spinal cord
- Spinal reticular zone, 234f. *see also* Spinothalamic and spinoreticular tracts
- Spinal shock syndrome, 238b
- Spinal tap, 80b
- Spinocerebellar pathways  
 clinical point, 358b  
 in somatosensory system, 358, 358f
- Spinothalamic and spinoreticular tracts, 83f, 356f  
 clinical point, 361b  
 sensory processing in spinal cord, 362–363, 362f  
 somatosensory systems of, 360f, 361–362
- Spinothalamic/spinoreticular anterolateral system, 235  
 damage to, 236b
- Spiny granule cell neuron, 337f
- Spiral (helical) scanners, 60
- Spiral organ. *see* Organ of Corti
- Splanchnic nerves, 211, 211f, 422f  
 development of, 130, 130f
- Splanchnopleure, 130
- Splenium, of corpus callosum, 58f  
 in axial (horizontal) section, 310, 310f–311f  
 in coronal section, 334, 334f–335f  
 in sagittal view, 343f
- “Split-brain” surgery, 322b
- Stellate cell neuron, 337f
- Stem cells  
 in CNS, intrinsic and extrinsic mechanisms of, 13, 13f  
 therapy, 14, 14f
- Stomach, and duodenum, innervation of  
 autonomic, 216, 216f
- Straight gyrus, 58f
- Straight sinus, 55f, 119–120
- Stretch reflex, 244, 244f  
 central control of, 246  
 clinical point, 246b
- Stria terminalis, 65b, 69  
 bed nucleus of, 283f
- Striatopallidal connections, 418
- Striatum, 416  
 efferents to, 283f
- Strokes, types of, 102, 102f
- Subarachnoid fluid system, 55
- Subarachnoid hemorrhage, due to ruptured aneurysm, 104b
- Subarachnoid space, 81f, 82
- Subcortical forebrain, 55  
 and human behavior, 341b
- Subdural hematoma, 49, 50f, 116b
- Subependymal veins, 120f
- Subfornical organ, 436, 436b, 436f
- Subfrontal hematoma, 50f
- Subgranular zone, of dentate gyrus, 13, 13f
- Subiculum, 451–452  
 inputs to, 453f
- Submandibular ganglion, 204, 205b, 422f  
 autonomic innervation through, 208, 208f
- Submucosal plexus, enteric, 221
- Substance P, 201
- Substantia gelatinosa, 234, 234f–239f
- Substantia nigra, 58f, 282f  
 in coronal section, 326, 326f–327f  
 neurochemistry in, 417
- Subventricular zone, of lateral ventricles, 13, 13f
- Sudomotor fibers, 210
- Sulcus, of brain, 52  
 medial surface of, 55f
- Sulcus limitans, 128, 150
- Summation, of excitatory and inhibitory inputs, 30
- Sunderland classification, of nerve injury, 159f
- Superficial cerebral veins, 116–117, 117f
- Superior cerebellar artery (SCA), 109
- Superior cerebral vein, 116f
- Superior cervical ganglion (SCG), 203b, 205b, 206
- Superior colliculus, 55f, 58f, 69, 264f  
 afferents to, 283f  
 in coronal section of forebrain, 332f–333f  
 mid-brain cross-section at, 259f  
 and tectospinal tract, 405b
- Superior longitudinal fasciculus, 342f  
 color imaging of, 343f–344f
- Superior medullary velum, 55f
- Superior parietal lobule, 53f
- Superior sagittal sinus, 55f, 116–117, 116b, 121  
 thrombosis in, 123b
- Supplemental motor cortex, 53f, 57f
- Supraoptic nuclei, 292f, 425
- Sweat glands, innervation of, 210
- Swinging flashlight test, 203b
- Sylvius, aqueduct of. *see* Cerebral aqueduct
- Sympathetic chain ganglia, 82, 199f, 422f  
 collateral, abdominal nerves and, 214  
 lumbar, abdominal nerves and, 214  
 thoracic, and splanchnic nerves, 211, 211b, 211f
- Sympathetic nervous system (SNS). *see also* Autonomic nervous system (ANS)  
 distribution of  
 in abdominal, 214, 214f  
 in adrenal gland, 225, 225f  
 in head and neck, 203, 231, 231f  
 in heart, 213, 213f  
 in immune system and metabolic organs, 199, 199f  
 in kidneys and upper ureter, 229, 229f  
 in liver and biliary tract, 223, 223f  
 in pancreas, 224, 224f  
 in pelvic nerves and ganglia, 227, 227b, 227f  
 in small and large intestines, 218, 218f  
 splanchnic nerves in, 211, 211f  
 in stomach and duodenum, 216, 216f  
 in tracheobronchial tree, 212, 212f  
 in urinary bladder, 228, 228f  
 preganglionic neurons of, 165, 202
- Sympathetically maintained pain, 363–364, 363b, 363f

- Synapses, 6, 6f  
 acetylcholine, 42f, 43  
 adrenergic, 201, 201f. *see also*  
   Norepinephrine  
 amino acid, 42f, 43  
 catecholamine, 42f, 43. *see also*  
   Norepinephrine; Serotonin  
 cholinergic, 201, 201f. *see also*  
   Acetylcholine  
 configurations of, 6b  
 growth of, 35b  
 inhibitory, 29  
 morphology of, 35, 35f  
 peptide, 43  
 serotonin, 42f, 43  
 strength of, regulation of, 39, 39f  
 Synaptic trough, 170f  
 Syringobulbia, 237b  
 Syringomyelia, 237b
- T**  
 Taste buds, receptors in, 367, 367f  
 Taste pathways, 368, 368f  
   clinical point, 368b  
 Tear production, 204  
 Tectospinal tract, 83f, 235f, 405, 405f  
   superior colliculus and, 405b  
 Teeth, innervation of, 272, 272f  
 Tegmentum, 142  
 Telencephalon, 295–352. *see also* Forebrain  
   adult derivatives of, 142, 142f  
   at 2 months, 137f  
   at 6 months, 138  
   at 36 days, 135, 135f  
   at 49 days, 136, 136f  
   comparison of, at 5.5 weeks and adult, 140f  
 Temperature sensory pathways  
   in spinothalamic and spinoreticular tracts,  
     361–362  
   spinal cord processing of, 362–363  
   trigeminal, 365f  
 Temporal bone, 46f  
 Temporal excitatory summation, 30, 30f  
 Temporal fossa hematoma, 50f  
 Temporal lobe, 52f  
   clinical point, 300b, 388b–389b  
   visual pathways in, 389, 389f  
 Temporal pole, 52f, 58f  
 Tendon organ reflex, 244f  
 Tentorium cerebelli, 118  
 Thalamic syndrome, 70b  
 Thalamus, 64, 142  
   anatomy of, 69, 69f, 290  
   caudal, in axial (horizontal) section of,  
     304, 304f–305f  
   clinical point, 290b, 330b  
   efferents to, 283f  
   interconnection with cerebral cortex and,  
     290, 290f  
   mid-, 306, 306f–307f, 328, 328f–329f  
   midsagittal view of, 55f, 57f  
   nuclei of, 70, 70f, 282f, 290, 330b  
   reticular nucleus of, 282  
   retinal projections to, 386, 386f  
   thalamocortical radiations, 290f  
   venous drainage of, 119, 119f  
 Thermoregulation, hypothalamus in, 442,  
   442f  
 Thoracic nerves, 180, 180f  
 Thoracic spinal cord, gray matter  
   organization in, 235  
 Thoracic sympathetic chain, and splanchnic  
   nerves, 211, 211f  
   clinical point, 211b  
 Thyroid-stimulating hormone (TSH), 438f,  
   439, 439b  
 Tibial nerve, 196, 196b, 196f  
 Tic douloureux, 271b  
 Time-of-flight phenomena, 107  
 Touch. *see* Epicritic sensation  
 Tracheobronchial tree, autonomic innervation  
   of, 212, 212f  
 Transverse sinus, 121, 123  
 Tremor, 304b  
 Tricyclic antidepressants, 347b  
 Trigeminal motor nuclei, 256f  
 Trigeminal nerve (CN V), 176, 263f  
   clinical point, 271b, 420b  
   divisions of, 176, 271  
   motor nuclei of, 256f  
   motor nucleus of, 394f  
   orbital, 267–268  
   sensory nuclei of, 256f  
 Trigeminal neuralgia, 271b  
 Trigeminal sensory system, 365–366, 365f  
 Trochlear nerve (CN IV), 263f, 394f  
   and ciliary ganglion, 269, 269f  
   clinical point, 268b  
   orbital, 267  
   in pons/mid-brain, 257f  
 Trunk, somatic innervation of  
   brachial plexus and, 181  
   lumbar plexus, 191, 191f  
   sacral and coccygeal plexuses in, 192,  
     192f  
 TSH. *see* Thyroid-stimulating hormone  
   (TSH)  
 Tuber cinereum, 55f, 58f
- U**  
 Ulnar nerve, 190, 190f  
 UMNs. *see* Upper motor neurons (UMNs)  
 Uncinate fasciculus, 342f  
   color imaging of fibers in, 344f  
 Uncus, 56f, 58f  
 Unipolar sensory cell, 7f  
 Unmyelinated axons  
   action potential in, 25  
   conduction of action potentials in, 26,  
     26f  
   myelination of, 19  
   somatosensory afferent, 356  
 Unmyelinated fibers, 7f  
 Upper limb  
   dermatome of, 182, 182f  
   somatic innervation of  
     cutaneous, 184, 184f  
     median nerve, 188, 188f  
     scapular, axillary, and radial nerves,  
       185, 185f  
     ulnar nerve, 190, 190f  
 Upper motor neuron (UMN) syndrome, 399b
- Upper motor neurons (UMNs), 164, 164f,  
   395–408  
   in central control of eye movements, 407,  
     407f  
   and central control of muscle stretch  
     reflex, 246b  
   in central control of respiration, 408, 408f  
   cerebellar efferent pathways to, 415, 415f  
   clinical point, 6b–7b  
     bulbar palsy and pseudobulbar palsy,  
       249b  
     decorticate posturing, 420b  
     pontine hemorrhage, 255b  
     upper motor neuron syndrome, 399b  
   in cortical efferent pathways, 395, 395f  
     color imaging of, 396  
     corticobulbar tract, 397, 397f  
     corticoreticular tract, 404, 404f  
     corticospinal tract, 398f, 399  
     interstitiospinal tract, 405, 405f  
     reticulospinal tract, 404, 404f  
     rubrospinal tract, 401, 401f  
     tectospinal tract, 405, 405f  
     vestibulospinal tracts, 402f, 403  
   terminations of, in spinal cord, 400, 400f,  
     406, 406f  
 Urinary bladder, autonomic innervation of,  
   228, 228f, 230, 230b, 230f
- V**  
 Vagus nerve (CN X), 143, 203, 263f, 278f, 279,  
   394f  
   in brain stem, 252f  
   clinical point, 279b  
 Varicosities, 6f  
 Vascular endothelial growth factor (VEGF), 12f  
 Vascular smooth muscle, innervation of, 210  
 Vasoactive intestinal peptide (VIP), 204b  
 Vasomotor fibers, 210  
 Vasopressin, 440, 440f  
   clinical point, 440b  
   water balance and fluid osmolality  
     regulation by, 441, 441f  
 Venous phase, 121, 121f  
 Venous plexus, 124b  
 Venous sinus thrombosis, 118, 118b  
 Venous system, 116–124, 116f  
   of brain, 119, 119f  
     relationship to ventricles, 120, 120f  
   of brain stem and cerebellum, 123, 123f  
   carotid venograms of, 121, 121f  
   magnetic resonance venography of,  
     coronal and sagittal views, 122,  
       122f  
   of meninges and superficial cerebrum, 116  
   sinuses of, 118, 118f  
   of skull, 116  
   of spinal cord, 124, 124f  
   superficial, cerebral, meningeal, diploic,  
     and emissary, 117, 117f  
 Venous thrombosis, 120b  
 Ventral horn, of spinal cord, 234–235, 239f.  
   *see also* Lower motor neurons  
   (LMNs)  
 Ventral ramus, 82, 177f  
   migration of, 130



- Ventral root(s), 81, 239f, 243f  
 Ventral tegmental nucleus, 282f  
 Ventricles, 55f, 85–91  
   anatomy of, 86, 86f  
   in coronal forebrain section, 87, 87f  
   development of, 149, 149f  
   fourth, anatomy of  
     lateral view, 89, 89f  
     posterior view, 88, 88f  
   lateral, 87  
   magnetic resonance imaging of, axial and coronal views, 90, 90f  
   third, 87  
   venous drainage surrounding, 120f  
 Ventricular system, magnetic resonance imaging of, 62  
 Ventromedial (VM) nucleus, and sexual behavior, 426  
 Vertebrae, spinal nerve roots and related, 160, 160f  
 Vertebral artery, 95, 95b  
 Vertebrobasilar system, 98b, 109, 109b, 109f  
   angiographic anatomy of, 110, 110f  
   occlusive sites of, 111, 111f  
 Vertical columns, of cerebral cortex, 338, 338f  
 Vertigo, 370b  
 Vestibular nerve, clinical point of, 377b  
 Vestibular nuclei, 252f, 283f  
 Vestibular pathways, 377, 377f  
 Vestibular system, 376–378  
   receptors, 376, 376f  
 Vestibulocerebellar pathways, 414, 414f  
   clinical point, 414b  
 Vestibulocochlear nerve (CN VIII), 263f, 275, 275f  
   clinical point, 275b  
 Vestibulospinal tracts, 83f, 239f, 377, 402f, 403  
   clinical point, 403b  
   termination of, in spinal cord, 403  
 Vibratory sensation. *see* Epicritic sensation  
 Visceral motor neurons, 7f. *see also* Enteric nervous system  
   myelination of axons of, 19f  
 Visual association areas, of cortex, 53f  
   basal surface of, 59f  
   medial surface of, 57f  
 Visual evoked potential, 34, 34f  
 Visual field deficit  
   and lesions, 390  
   in optic nerve, 386b  
 Visual system, 379–390  
   cerebrovascular disease in, 384b  
   lesions of, 390, 390f  
 Visual system (*Continued*)  
   oculomotor nerve, clinical point of, 379b  
   optic chiasm and, 385, 385f  
   optic nerve in, 380, 383, 383f  
     clinical point, 380b  
   pathways of  
     clinical point, 386b  
     parietal and temporal lobes, 389  
     retino-geniculo-calcarine, 388, 388f  
     thalamus, hypothalamus, brain stem, 386, 386f  
   photoreceptors in, 382, 382f  
   retina in, 381  
     clinical point, 381b  
 Visual tecta, 55  
 Voltage-gated ion channels, 25f–36f
- W**  
 Wallenberg syndrome, 251b, 262f  
 Weber's syndrome, 260b, 262f  
 Wernicke aphasia, 346f  
 Wernicke-Korsakoff syndrome, 427b, 460b  
 Wernicke's area, 53f  
 White matter, of spinal cord, 83, 83f, 235  
 White ramus communicans, 200f–201f, 206f, 422f